Is transition from paediatric to adult healthcare with a life-limiting condition associated with more unplanned hospital care?

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1 Abstract

Life-limiting conditions, which shorten or threaten to shorten life, are becoming increasingly prevalent among young people in England, attributed partly to longer survival.

There are concerns about the transition from paediatric to adult healthcare.. Specialist paediatricians oversee childhood healthcare, with needed allied services provided continuously. A General Practitioner (GP) often coordinates adult healthcare; GPs may lack knowledge of the young person or condition. There can be provision gaps in allied services. Sometimes no equivalent adult service. These issues may lead to an increase in unplanned hospital care. Previous research is limited to a few more prevalent conditions and has used small, potentially unrepresentative, samples or used age to assign transition status, risking misclassification.

I aimed to determine whether there is an association between transition from paediatric to adult healthcare and increased unplanned hospital care for young people with life-limiting conditions, to understand the nature of the population, including changing medical complexity and to explore the role of primary care. I used secondary data analyses of routinely collected healthcare data in England and a systematic review. My research was the first to analyse healthcare use across the transition using national data with transition point estimated for each individual, using a newly-developed method.

I found the population of young people with life-limiting conditions transitioning to adult healthcare is growing in size and medical complexity, with more comorbidities and consultants of more different specialities involved. Evidence from previous studies was mixed and conflicting on changes in healthcare use at transition and there was a lack of UK studies. My research found unplanned hospital care increases for young people with life-limiting conditions after the transition and regular contact with the same GP is associated with reduced use of unplanned hospital care. The role of the GP should be considered in reforms to improve transition.

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5 Acknowledgements

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6 Author's declaration

The five papers forming this thesis are listed below together with details of my contribution to each publication. I confirm that the integrative chapter linking the papers is entirely my own work. I declare that this thesis is a presentation of original work and I am the sole author. This work has not previously been presented for an award at this or any other university. All sources are acknowledged as references.

Signed: Date: 27 May 2022

(Stuart Jarvis)

6.1 Contributions to papers

6.1.1 Jarvis, S., Richardson, G., Flemming, K. and Fraser, L., 2022. Numbers, characteristics, and medical complexity of children with life-limiting conditions reaching age of transition to adult care in England: a repeated cross-sectional study. *NIHR Open Research*, *2*, p.27.

Candidate contribution: Conceived the idea; designed the study; applied for data and gained ethical approval; carried out the analysis; wrote manuscript.

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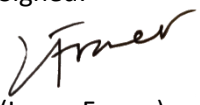

(Stuart Jarvis) (Lorna Fraser)

6.1.2 Jarvis, S.W., Roberts, D., Flemming, K., Richardson, G. and Fraser, L.K., 2021. Transition of children with life-limiting conditions to adult care and healthcare use: a systematic review. *Pediatric research*, *90*(6), pp.1120-1131.

Candidate contribution: Conceived the idea; designed the study; wrote the search strategy; carried out the search, screening and data extraction; wrote manuscript.

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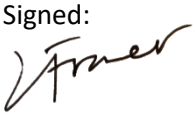

(Stuart Jarvis) (Lorna Fraser)

6.1.3 Jarvis, S., Richardson, G., Flemming, K. and Fraser, L., 2021. Estimation of age of transition from paediatric to adult healthcare for young people with long term conditions using linked routinely collected healthcare data. *International journal of population data science*, *6*(1).

Candidate contribution: Conceived the idea; designed the study; developed the estimation methods; applied for the data; carried out the analysis; wrote manuscript

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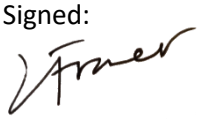

(Stuart Jarvis) (Lorna Fraser)

6.1.4 Jarvis, S., Flemming, K., Richardson, G. and Fraser, L., 2022. Adult healthcare is associated with more emergency healthcare for young people with life-limiting conditions. *Pediatric Research*, pp.1-12.

Candidate contribution: Conceived the idea; designed the study; applied for the data; carried out the analysis; wrote manuscript.

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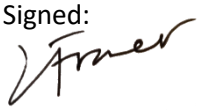

(Stuart Jarvis) (Lorna Fraser)

6.1.5 Jarvis, S., Parslow, R.C., Hewitt, C., Mitchell, S. and Fraser, L.K., 2020. GPs' role in caring for children and young people with life-limiting conditions: a retrospective cohort study. British Journal of General Practice, 70(693), pp.e221-e229.

Candidate contribution: Designed the study; developed the measures of GP contact; contributed to data application; carried out the analysis; wrote manuscript.

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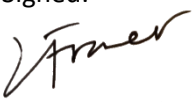

(Stuart Jarvis) (Lorna Fraser)

7 Introduction

This thesis presents the findings from a programme of research investigating the transition from paediatric to adult healthcare for young people with life-limiting conditions in the UK, with particular focus on changes in healthcare use post- compared to pre-transition. Life-limiting conditions have become increasingly prevalent among children and young people in the UK (Fraser et al., 2012, Fraser et al., 2015, Fraser et al., 2020a). As a group, they are more common than other conditions such as diabetes (2018: 97,000 children and young people with life-limiting conditions in England (Fraser et al., 2020b), compared to 40,000 with diabetes in the UK (Diabetes UK, 2019)). Given longstanding concerns about the transition to adult healthcare for young people with chronic conditions, as detailed below, and the growing population with life-limiting conditions, research into transition for this population is both timely and important.

The research is presented as five published papers, meeting specific research objectives set out below. This integrative chapter provides background information on young people with life-limiting conditions, previously identified problems with the transition to adult healthcare, existing research in this area and an overarching description of the methods used within the research. It summarises the findings of the papers, puts these in context with the wider literature and highlights the implications of the research and the questions that remain unanswered.

7.1 Life-limiting conditions: definition and context

Life-limiting conditions are conditions that lead to premature death or threaten to do so (Chambers, 2018). They can be split into four groups (Chambers et al., 2009) (Table 1). In North America the terms *complex chronic conditions* or *children with medical complexity* are often used to describe a similar population (Feudtner et al., 2000, Cohen et al., 2011). Hereafter, studies relating to life-limiting conditions, complex chronic conditions and children with medical complexity are all considered relevant. Except where a distinction is made between the various definitions, the term life-limiting conditions is used throughout.

Table 1: Categories of life-limiting conditions, adapted from (Chambers et al., 2009).

Category 1	Life-threatening conditions - e.g. cancers, organ failure
Category 2	Conditions for which premature death is inevitable - e.g. cystic fibrosis, Duchenne muscular dystrophy
Category 3	Progressive conditions without curative treatment options - e.g. Batten disease, mucopolysaccharidoses
Category 4	Irreversible, but non-progressive conditions leading to susceptibility to other health conditions and likelihood of premature death - e.g. severe cerebral palsy

The number of children with life-limiting conditions has been increasing, attributed, at least in part, to increasing survival (Fraser et al., 2020a) and there is evidence for increasing survival times for specific conditions (Eagle et al., 2002, Van Ruiten et al., 2016, Cravelle et al., 2012, MacKenzie et al., 2014, Blair et al., 2019). As survival times increase for conditions that, in the past, commonly caused death during childhood, more children with life-limiting conditions reach adulthood and experience the transition from paediatric to adult healthcare.

7.2 Transition to adult healthcare

Secondary healthcare providers are usually different for children and adults, both in the UK and in other countries, and paediatric healthcare is recognised as distinct from adult healthcare (Wolfe et al., 2016, Committee On Pediatric Workforce et al., 2015, Sawyer et al., 2019). For children with life-limiting conditions, care in childhood is typically overseen by one or more paediatric specialists and allied services such as physiotherapy are provided as needed on an ongoing basis (Care Quality Commission, 2014, White and Cooley, 2018). Adult care is often coordinated by a General Practitioner (GP) and allied services have to be booked in blocks with the potential for a gap in provision (Care Quality Commission, 2014, Lemer, 2013).

Due to the division between paediatric and adult care, a transition is required at some point. In the UK, this has typically been at age 16 years for most young people - e.g. a child under 16 years requiring acute hospital treatment would tend to be admitted to a paediatric ward, while a young person aged 16 years or over may be admitted to an adult ward, although policies do vary by NHS Trust and wards within Trusts (Royal College of Paediatrics and Child Health, 2017). For young people with on-going healthcare needs, transition has been more flexible, with a conscious decision to transfer care from paediatric to adult services and, ideally, a transition process involving both services (Willis and McDonagh, 2018). As such, transition age varies, although it is

targeted to take place from 16 to 19 years, with preparation beginning around 14 years (Willis and McDonagh, 2018, Care Quality Commission, 2014).

The requirement for transition to adult services for many chronic conditions, such as diabetes, has been recognised for many decades. For these conditions, there has been extensive research into transition and interventions to aid successful transition (Sheehan et al., 2015, Allen et al., 2012, Allen et al., 2010, Hale and Hargreaves, 2017, Nakhla et al., 2009, Price et al., 2011). For some life-limiting conditions, it was, until relatively recently, common for many children to die while still under paediatric healthcare. As treatments have advanced, survival times have increased and more children are surviving into adulthood (Landfeldt et al., 2020, Best and Rankin, 2016). Therefore, increasing numbers of children with life-limiting conditions are undergoing transition to adult healthcare. This has exposed a number of concerns around transition:

- Lack of planning, which can make the transition appear abrupt (Goodman et al., 2011, Care Quality Commission, 2014, Lugasi et al., 2011, National Institute for Health and Care Excellence, 2016, Fegran et al., 2014).
- Variations in transition planning and support between conditions and even between service providers for the same conditions (Care Quality Commission, 2014, Doug et al., 2011).
- Lack of training for GPs and a lack of familiarity with the children and their, sometimes, very rare conditions (Lemer, 2013, Hudson et al., 2014, Doug et al., 2011).
- Lack of continuity in services (Care Quality Commission, 2014, Heery et al., 2015).
- An absence of adult equivalents of some paediatric services, such as community services for complex neurological conditions (Kirk and Fraser, 2014, Tilton, 2018, Oskoui and Wolfson, 2012).

Living with a life-limiting condition is extremely challenging, for young people and their families, with impacts on mental health, income and expenses (DiFazio and Vessey, 2013, Kirk and Fraser, 2014, Clark et al., 2017, Commodari, 2010, Fiorentino et al., 1998, Kuo et al., 2011). Young people with life-limiting conditions also represent challenges for healthcare services: they are typically high users of healthcare and often have complex needs (Ananth et al., 2015, Berry et al., 2011, Berry et al., 2013, Bramlett et al., 2009, Cohen et al., 2012, Cohen et al., 2011, Feudtner et al., 2002, Feudtner et al., 2003). It is therefore important to make the transition from paediatric to adult healthcare as good as possible to avoid exacerbation of these challenges.

The idea for this PhD arose from discussions with families, particularly at the Martin House Research Centre consultation with stakeholders about research priorities (Beresford et al., 2017,

Booth et al., 2018). The issues raised by families were that there are many potential negative consequences associated with the transition which may lead to worse condition management and, either due to deteriorating conditions or a lack of trust in primary care, in additional visits to hospital for emergency healthcare. Many identified a lack of regular GP contact and a lack of consistency in the GP seen as barriers to developing trust and confidence in primary care services. Emergency hospital care may have negative implications for the young people themselves, due to disruption to lives, travel away from family and support networks and possible emotional trauma from emergency treatment (Compas et al., 2012, Findlay et al., 2008). There are also potential impacts on parents and other family members whose lives (work, education etc.) may also be disrupted by additional hospital visits and whom may experience additional emotional strain (Franck et al., 2015, Commodari, 2010, DiFazio and Vessey, 2013, Wray et al., 2011).

It is important for healthcare providers and policy makers to have a good understanding of the size and nature of the population of young people with life-limiting conditions who reach transition to adult care and the possible impacts of transition on healthcare use to provide suitable services, now and in the future.

7.3 Limitations of existing research

While there is previous research on young people with life-limiting conditions and the impacts of transition, raising many concerns as outlined above, there are some important gaps and limitations.

There have been studies estimating the current prevalence of life-limiting conditions and these include young people at ages at which transition is likely to take place (Fraser et al., 2020b, Fraser et al., 2020a, Fraser et al., 2012, Jarvis et al., 2016). However, these studies have not differentiated between those diagnosed in childhood (likely to undergo transition to adult healthcare) and those diagnosed in adulthood (likely to go straight into adult healthcare). There are, therefore, no estimates of the number of young people with life-limiting conditions likely to be undergoing transition to adult care, so there is a lack of information on national demand for transition services in this population. There is also a lack of information on the diagnostic profile, demographics or medical complexity of this population at transition age, all of which are important for service planning.

Pre-existing systematic reviews considering healthcare use at transition have tended to be focused on one or a few of the more specific life-limiting conditions, such as cystic fibrosis (Coyne et al., 2017, Coyne et al., 2016, Dallimore et al., 2018, Girgenti, 2015, Heery et al., 2015). There is a lack of reviews including the less prevalent conditions. This is important as the more commonly

studied conditions, such as cystic fibrosis and cancer, account for only a minority of those with life-limiting conditions and have potentially very different prognoses with extended survival into adulthood being common (Saletta et al., 2014, Keogh et al., 2018). While it may not be practicable to study rarer conditions individually, there is value in research that covers a greater section of those with life-limiting conditions. Basing policy on cancer patients, for example, risks development of services that meet the needs of this small subsection of the population with life-limiting conditions, but ignore those of others. Therefore, the existing research may not be generalizable across all young people with life-limiting conditions. Studying all life-limiting conditions increases potential sample size and ensures that less common conditions are also represented.

Many previous studies have used data from a single clinic or insurance provider, possibly limiting generalisability. Those that have used large, representative datasets have used a simple age-cut off to assign transition status, with a risk of misclassification bias.

Finally, some studies have highlighted the importance of primary care and suggested that a lack of expertise and familiarity with conditions and young people with life-limiting conditions in primary care may exacerbate problems experienced at transition (Bhawra et al., 2016). However, there is a lack of research considering what good primary care might look like for this population or linking this to healthcare outcomes and use. Without an understanding of this, it will be hard for primary care to develop to better serve this population.

7.4 Aims and objectives

This research aimed to determine whether there is an association between transition from paediatric to adult healthcare and increased emergency hospital care for young people with life-limiting conditions, to understand the nature of the population and to explore the role of primary care. It has the following specific objectives, each addressing an identified gap or limitation in previous research:

1. Assess national trends in the numbers, characteristics, and medical-complexity of young people with life-limiting conditions reaching the age to transition to adult healthcare in England.
2. Review the existing evidence for a change in health or social care use for young people with life-limiting conditions post- compared to pre-transition.
3. Determine the feasibility and implications of estimation of transition age from routinely collected health data.

4. Establish whether there is an increase in emergency inpatient admissions and Emergency Department visits when children in England with life-limiting conditions transition to adult healthcare using a nationally representative dataset.
5. Assess the association between face-to-face GP surgery consultations and emergency healthcare use in children and young people with a life-limiting condition.

The research is presented as a series of papers, one for each of the above objectives. The common methodologies, links between them, relationships with previous research and implications for future research and policy are set out below.

8 Methods

Detailed methods are reported in each of the papers. Apart from the systematic review, the other papers are secondary analyses of routinely collected healthcare data. This approach and the data sources are briefly introduced here, before the fuller implications of this approach are addressed in the Discussion section.

8.1 Routine healthcare data

Although a substantial population overall, children and young people with life-limiting conditions are still a small part of the overall population (Fraser et al., 2020a). I used routinely collected healthcare data to ensure large sample size compared to using data from a single clinic, like many previous studies, but also to use data representative of the general population (Herbert et al., 2017).

The sources of routinely collected data used in my research were the Clinical Practice Research Datalink (CPRD) GOLD (Herrett et al., 2015) and Hospital Episodes Statistics (HES) (Herbert et al., 2017). CPRD includes primary and secondary care data for a subsample of the population. As of 2015, approximately 6.9% of the UK population, stated to be broadly nationally representative were contained in CPRD GOLD (Herrett et al., 2015) and this increased to around 8% by 2017 (Kontopantelis et al., 2018). However, the nature of primary care datasets in the UK is that they are derived from data held by individual companies providing software database systems to primary care practitioners and there is substantial clustering of providers by geographical region, meaning that the data from any one system may not be geographically representative (Kontopantelis et al., 2018).. HES provides whole population secondary care data. The data available from each source are summarised in Figure 1. HES data typically contained three categories of healthcare records: inpatients, outpatients and Accident and Emergency

Department (A&E) data. ONS death registration records could also be linked. CPRD data typically included separate datasets for lists of patients, practices, staff, consultation data (e.g. date, time, type, staff involved), clinical data (e.g. diagnoses) and referral data to other services. Deprivation data, Office for National Statistics (ONS) death registration data and HES data were also available for inclusion as linked data. Deprivation data in the CPRD data were in the form of Index of Multiple Deprivation (IMD) scores. The IMD are area based measures of deprivation, comprising scores over seven domains - income, employment, health, education, housing, crime and environment - with an overall score a weighted combination of individual domain scores (Smith et al., 2015). The IMD are frequently updated and the most recent available were provided for each CPRD dataset, meaning the IMD 2015 were used (Smith et al., 2015). Within CPRD data, IMD are available for both the LSOA of the practice at which a patient is registered and for the LSOA of the patient's last known home address. The latter was used for the studies described herein as deprivation levels for individuals was of greater interest than deprivation levels at locations of practices. Often, the two may be the same or similar if a patient lives in close proximity to a practice, but a practice could be located in an area of very different deprivation to a patient's home address. Within HES data from NHS Digital, LSOA of residence was provided directly and the most recent available IMD was applied based on this.

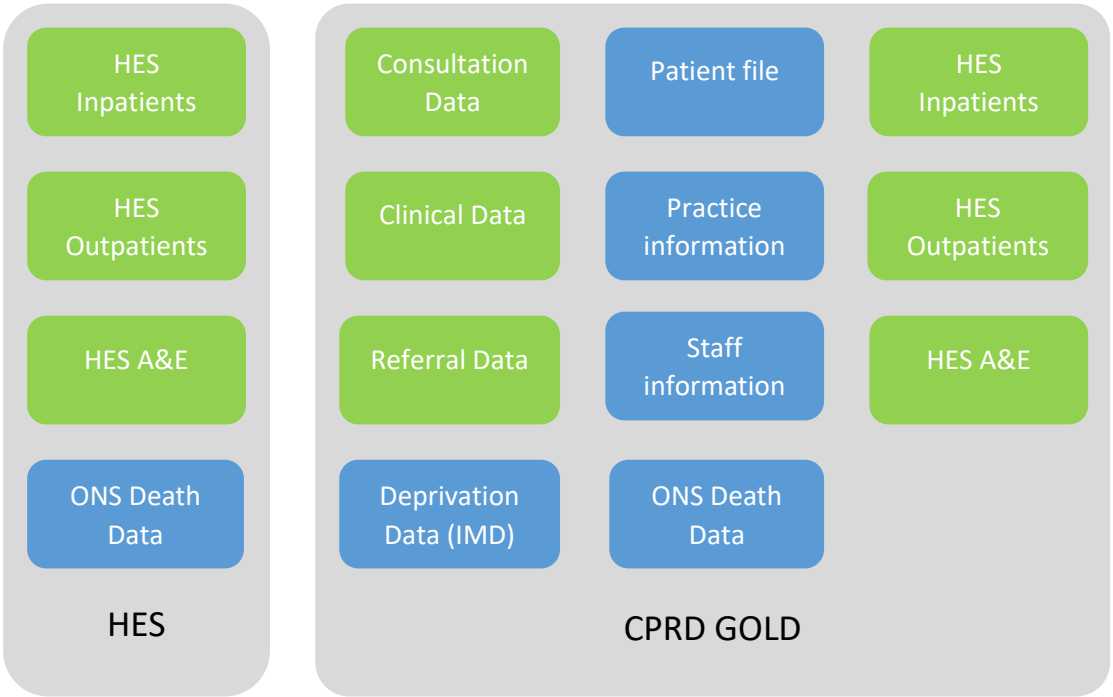

Figure 1: Typical included data files for Hospital Episodes Statistics (HES) and Clinical Practice Research Datalink (CPRD) GOLD data requests used in this PhD - green: healthcare records;

blue: administrative - e.g. Office for National Statistics (ONS) death registration data - and demographic data.

For analysis of numbers of healthcare events, it was important to know the time for which each person was at risk of the healthcare event occurring. This could be determined from the CPRD data (start and end dates of registration with a GP are recorded) but for HES data only inferred from hospital visits. A person absent from HES data in a year may still be resident and have had no hospital contact or may no longer be resident in England and so not at risk. For objective 1 (describing the population with life-limiting conditions and its medical complexity) time at risk was less important and the larger sample size of HES enabled analysis of differences between groups of conditions. For objectives 4 and 5, time at risk was important (and, for objective 5, primary care data were also essential) so CPRD data were used. There are now two primary care datasets available from CPRD: GOLD and Aurum, based on different data providers. At the time of writing, Aurum is by far the larger dataset and, although it, like GOLD, suffers from issues of geographical generalisability due to distribution of contributing practices (as described above) the larger sample size would have been advantageous in analysing the relatively small population of children and young people with life-limiting conditions. If the research described in this thesis was repeated today, Aurum would be used. However, when applications for data for these studies were first made, Aurum was a relatively new dataset. A data resource profile was first published in March 2019, with no published studies using Aurum at that point (Wolf et al., 2019). The study herein exploring the role of GP care for children and young people with life-limiting conditions (paper 5) used data for which the application was made in 2016, before Aurum was announced. The data for studies described in papers 3 and 4 was first applied for in 2019. Given familiarity with GOLD from previous research and a lack of completed studies using Aurum at that point, it was chosen to continue to use GOLD for these studies.

The analytical approach taken in my papers, except for the systematic review, was secondary data analysis. For objectives 3 to 5 I was interested in finding the transition point and/or assessing healthcare use for a group of young people with life-limiting conditions. For these, I used retrospective cohorts, identified using previously developed coding frameworks for life-limiting conditions (Fraser et al., 2012). For objective 1, I was not concerned with following a single group through time and assessing outcomes in relation to exposures, so I instead used a repeated cross-section design, including, in each year, any individuals meeting the inclusion criteria, based on age and diagnoses.

8.2 Patient and public involvement

A common feature across the studies in my PhD research was public and patient involvement through the Martin House Research Centre Family Advisory Board (FAB). This forms a key part of the Centre's Public Involvement and Engagement strategy (Martin House Research Centre, 2019). Established in 2018, it comprises parents and other adult family members of children with life-limiting conditions and meets regularly with researchers from the Centre. At these meetings, researchers update on progress on ongoing research and new studies and seek input into research. FAB members have the opportunity to raise their own suggestions for areas of interest and to provide feedback on findings and planned research. A decision was made early on, during the application for Fellowship funding, to consult with parents and carers at multiple stages of the research, to develop a better understanding of the context of healthcare transition and ensure the research considered relevant issues.

The FAB was consulted three times during the course of my PhD. Their experience and insights influenced the direction of research and interpretation of findings. Specifically, input from the FAB led directly to the following:

- A decision to adopt broad inclusion criteria for the systematic review (paper 2), with any change in healthcare at transition being included, due to FAB input that healthcare use changes extend beyond emergency care and increases in numbers of outpatient appointments could be common, particularly where one paediatric specialist was replaced with multiple adult specialists.
- The choice of estimation methods assessed in paper 3 and the recommendation for a preferred method - FAB members reported that transition was not always clear cut, but it was uncommon to see any paediatric specialists after the point of transition, while adult specialists might be seen before transition.
- The inclusion of a group without any long-term conditions in analyses of changes in healthcare use at transition (paper 4) due to the FAB highlighting that many other transitions happen at a similar time, e.g. changes in education and, potentially, residence.
- An understanding of the importance of primary care and, in particular, the benefits of consistently seeing and building up a relationship with a single GP, something assessed in paper 5.

A number of other insights aided interpretation of results and reinforced issues already reported in the literature, informing discussion sections of the papers. These included:

- Fragmentation in adult care, with FAB members finding it necessary to explain to different clinicians the need for services that were provided pre-transition.
- Experiences of gaps and waits for provision in adult care.
- Reduced parental access to adult hospital wards, preventing them from giving their children the level of support they had been accustomed to in paediatric wards.

9 Results - Research papers

The papers presented in this thesis are interlinked, with each depending on and informed by the findings of the others. The papers are described below. Their relation to the objectives, to each other and to the data sources used are also illustrated in Figure 1.

9.1 Paper 1: Numbers, characteristics, and medical complexity of children with life-limiting conditions reaching age of transition to adult care in England: a repeated cross-sectional study (objective 1)

Good service provision for young people with life-limiting conditions transitioning to adult healthcare is dependent on a good understanding of the size, nature and complexity of this population (Care Quality Commission, 2014). As noted in the introduction, there is a lack of research providing this information.

The first paper (Jarvis et al., 2022a) aimed to meet objective 1 by estimating the number of young people in England with a life-limiting condition diagnosed in childhood reaching ages at which transition to adult care takes place, their demographics and their medical complexity (a multi-faceted concept indicative of healthcare and technology needs and impacts on families (Cohen et al., 2011)). Demographics and medical complexity are useful for targeting services, ensuring that they are well matched to users and understanding whether needs per person are increasing or decreasing (Cohen et al., 2012, Yu et al., 2021).

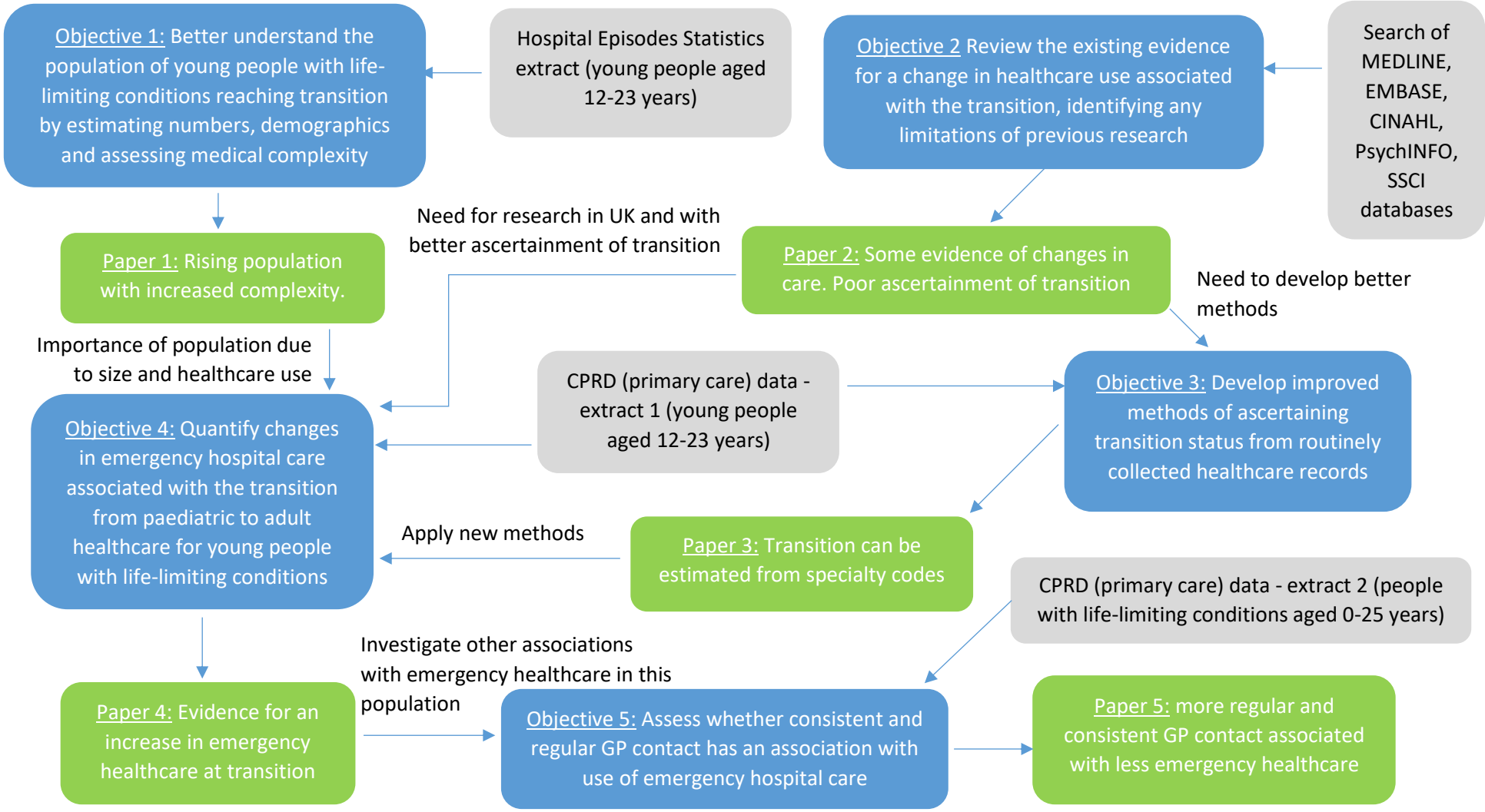

Figure 2: Relationships between objectives (blue), data sources (grey) and papers (green)

The paper addressed these questions using an extract of national HES data. HES was preferred as, being whole population, it was better suited than CPRD for drawing inferences about geographical distributions. CPRD, while broadly representative, has an uneven geographic spread with, for example, fewer participants in Yorkshire and the Humber than in other regions (Herrett et al., 2015, Kontopantelis et al., 2018). Primary care data were not critical for this study and it was expected that the vast majority of young people with life-limiting conditions would have at least outpatient hospital care each year, so there was little risk of underestimating the population actively receiving healthcare by using only HES data. The study used existing coding frameworks (Fraser et al., 2012) to identify young people with life-limiting conditions identified in childhood and then counted those aged 14-19 years in each financial year from 2012/13 to 2018/19. Numbers of young people with life-limiting conditions were reported rather than prevalence for two reasons. First, the paper explicitly aimed to inform healthcare provision, particularly at the transition from paediatric to adult healthcare. Here, it is more important to know the number of young people with these healthcare needs than the prevalence (e.g. per 10 000 population) as the resource used is determined by number of healthcare users (and their individual needs). A secondary consideration was that the research was conducted during the year in which a new census was being conducted, so the most recent definitive population figures were around a decade out of date. While mid-year population estimates are available, these are imperfect and may be impacted by events such as Brexit and the Covid-19 pandemic, meaning there would be uncertainty in the denominator used in prevalence estimation. The 14-19 years criterion was used to identify individuals who would be likely to be either in the early stages of transition planning, undergoing transition or in the first few years post transition (Care Quality Commission, 2014) i.e. a population for whom service providers should be providing transition support.

The study found a greater rate of increase in numbers of 14-19 year olds with life-limiting conditions diagnosed in childhood than previously reported for 14-19 year olds with life-limiting conditions as a whole (diagnosed as children or as adults) (Fraser et al., 2020a). This is important for healthcare transition planning as those diagnosed with a life-limiting condition as an adult (i.e. after age 16 years) may go straight into adult healthcare and so not undergo a transition from paediatric to adult healthcare. Relying on estimates of changes in numbers of 14-19 year olds with life-limiting conditions from previous studies would underestimate the increasing demand for transition services.

The reported changes in numbers were quite startling, increasing by 68%. This is comparable with some other studies looking at numbers of children and young people with life-limiting conditions

(Fraser et al., 2012, Jarvis et al., 2016) but it should be noted, in common with those studies, that the reported increases may not be entirely reflected in increases in the number of young people with life-limiting conditions in the population. Numbers from earlier years may be underestimates, as young people with life-limiting conditions are only detected when they have a hospital record with a relevant diagnosis - young people in a stable stage of condition without hospital attendance may be missed for a number of years. Related to this, changes in data recording and - particularly - more complete recording of relevant diagnoses over time could also lead t reported numbers increasing more rapidly than real prevalence in the population. There are also potential issues with specificity of the coding framework, which may mean that not all people included have life-limiting conditions so that the overall numbers could be an over estimate.

There were differences in changes in size of the transition population between regions. There were also larger increases in the population within non-White ethnic groups, underlining the importance of culturally appropriate transition and adult services. Finally, the study found indications of increasing complexity in terms of numbers of chronic conditions (including life-limiting conditions) and the number of distinct main specialities of consultants involved in care for the population with life-limiting conditions reaching transition ages. This is likely to make transition more challenging for young people and service providers as more different services are involved in care and multiple transitions take place. While there was limited evidence for increased healthcare use per person over time, the increasing size of the population - which has high healthcare use in general - points towards increasing demand for healthcare.

The paper also had some findings in common with an earlier single centre study (Horridge et al., 2016) with young people most likely to have relatively low numbers of reported indicators of complexity, but a substantial minority having many more indicators of complexity.

The research also has wider relevance in being the first study to operationalise concepts of medical complexity in routinely collected healthcare data in England, making reproducible assessments of medical complexity possible without primary data collection or detailed medical notes review. The approach could be applied to other populations - e.g. those with other chronic conditions.

9.2 Paper 2: Transition of children with life-limiting conditions to adult care and healthcare use: a systematic review (objective 2)

Although there have been previous studies looking at healthcare use around transition for young people with chronic conditions; few have looked specifically at life-limiting conditions. Many studies looked at interventions to improve transition and compared outcomes before or after interventions were introduced or used trial designs.

I conducted a systematic review (Jarvis et al., 2021b) that assessed the evidence for changes in healthcare use post- compared to pre-transition in Organisation for Economic Co-Operation and Development (OECD) countries. While previous systematic reviews have looked at transition for young people with life-limiting conditions, they have mainly focused on experiences, interventions and biological indicators of disease progression rather than healthcare use and focused on a few of the more common conditions. Reviewing the evidence on healthcare use was important to avoid duplication of previous work in my research and to identify gaps in knowledge or limitations in methodology. The review had broad inclusion criteria, reflected in the search strategy, considering evidence for any healthcare use or social care use or cost outcome, apart from those that were purely prescribing data. This was to increase sensitivity to try and capture as much as possible of the evidence in this area. Evidence was considered from all OECD countries from studies published from 1990 onwards.

The reported outcomes, from eighteen included studies, covered outpatient attendance, inpatient admissions, Emergency Department visits, inpatient bed days, intravenous antibiotics, physiotherapy, access to HIV care, GP contact and healthcare costs. However, outcomes were focused on outpatient attendance and inpatient admissions (eleven and ten studies, respectively, with no more than five studies for any other outcome). Studies were also dominated by some of the more common life-limiting conditions (five for cystic fibrosis, four for renal conditions, three for cerebral palsy). Other neurological conditions, despite affecting 12% of children with a life-limiting condition and a major referral group for paediatric palliative care, were under-represented. Most studies were from North America and only one was from the UK.

Evidence was mixed and conflicting, particularly for the more commonly reported outcomes of outpatient attendance and inpatient admissions. There were some differences by country (where there were sufficient studies to draw conclusions about differences between studies in different countries being larger than differences between studies from a single country, i.e. comparing Canada and the United States). Given the conflicting evidence and limited number of life-limiting conditions represented, no clear conclusions could be drawn about the associations between transition and most types of healthcare use. Use of a meta-analysis to pool results was rejected due to the differences in research questions of papers, outcomes considered and settings. While pooling is always possible, it would not have been meaningful to produce a pooled estimate for any of the outcomes covering different countries where effect direction for transition appeared to be opposite. Even for countries with multiple studies (e.g. United States, Canada) the differences in settings were such that I did not consider it useful to conduct a meta-analysis. There was however evidence for

increases in emergency department visits after transition, one of the aspects of emergency care use of primary interest for my research.

The review also showed that the studies fell largely into two groups. There were small studies from a single or small group of clinics which had the advantage of a well-defined transition point from paediatric to adult care: transfer of a young person from a paediatric to adult clinic or from a paediatric to adult clinician within the same clinic. However, as noted in the introduction, the findings from these studies could lack generalisability as the clinic population could be unrepresentative of the wider population due to geographical location, with a catchment population differing to the general population or, in healthcare systems that were not single payer, due to healthcare use differing between those with different health insurance provision. There were also larger studies, using national data either from healthcare records or from condition-specific registries. These, however, lacked information on when a young person transitioned from paediatric to adult care and so generally used an age-based cut-off. Transition does not take place at a single age for all people, so there is a risk of misclassification bias.

The review identified evidence for an increase in emergency department use after transition. It reinforced the importance of studying changes at the transition across a full range of life-limiting conditions, the lack of UK-based research and highlighted the need for a better method of ascertaining, from routine healthcare records, whether a young person was in paediatric or adult care.

9.3 Paper 3: Estimation of age of transition from paediatric to adult healthcare for young people with long term conditions using linked routinely collected healthcare data (objective 3)

The third paper (Jarvis et al., 2021a) addressed the limitations in preceding research exposed by the systematic review around ascertainment of transition status. In studies that used large datasets without access to detailed clinical records, age was generally used as a cut-off for assignment to pre- and post-transition groups, with a risk of misclassification bias. This paper aimed to meet objective 3, developing improved methods of ascertaining transition status from routinely collected healthcare records in England.

A previous scoping review (Shulman et al., 2020) found two main approaches to estimating transition: using the last paediatric visit and/or first adult visit (where recorded, e.g. in records from a single clinic) or using an age cut-off. It would be possible to estimate transition point from routinely collected healthcare data if there was some means of identifying healthcare visits as taking

place under either paediatric or adult care. Routinely collected hospital records available for research (e.g. HES) are not explicit in whether an episode of care is paediatric or adult, but information can be gleaned from the specialty codes recorded for inpatient and outpatient care. HES data record the treatment specialty and the main specialty of the consultant in charge of care and, from 2007 onwards, many of these (particularly treatment specialities) are classified as either paediatric or adult. At least some records could therefore be classified as specifically under either paediatric or adult care.

A classification system, defining treatment and consultant main specialities as paediatric, adult or unknown, was developed and applied to the data. The classification system was reviewed to check whether any 'adult' specialties were particularly common at ages at which young people were very unlikely to be in adult care (i.e. under 14 years). Such specialties were then reclassified as unknown, indicating neither paediatric nor adult care.

Three methods were then evaluated for estimating transition point from the classified records:

- using the last recorded paediatric record as the transition point
- using the first recorded adult record as the transition point
- using a statistical fitting approach to find a transition point that minimised the number of adult records before transition and paediatric records after transition

The results were taken back to the Family Advisory Board and there was further discussion on how meaningful each of the methods might be. Use of the first adult record was rejected based on the data and Board members' experiences. The data showed that many children had 'adult' records at young ages and the Board members reported that there might be isolated visits during childhood to services that were not paediatric specific. More consideration was given to the fitted and last paediatric record approaches, but it was felt that the last paediatric record marked a more meaningful transition point, as the completion of transition: it was unlikely, after transition had taken place that there would be further paediatric healthcare.

A question remained around the importance of estimating transition point from the data, rather than using an age cut-off: did the possible misclassification bias from use of an age cut off have a significant effect on detection of differences in outcomes pre- and post-transition in practice? This was explored through simulation, allocating to the study population simulated numbers of events for a healthcare outcome, based on each method of estimating transition. Regression analyses were then used to try and detect the change in event count at transition (set to 20% in the simulated data) using each of the transition estimation methods and an age cut-off at 16 or 18 years. Using an

age cut-off resulted in detection of changes at transition that were smaller than half that assigned. Such an approach could therefore compromise sensitivity of studies looking at healthcare changes at transition, leading to underestimation of such effects. It could potentially lead to conclusions of no significant effect depending on the power of the study - for example a study powered to detect changes of 20% in a healthcare outcome at transition might fail to find a significant difference in a population with a real change of 20% at transition, but a detected change of only 10% due to misclassification bias. It is, however, important to note that there is no gold standard available for objectively assessing performance of the estimation methods - there is no definitive answer as to what the transition status is for each individual in the data. The simulation therefore only shows that there is potential for estimation of transition point for each individual to improve sensitivity. The error associated with estimating transition (and associated potential for misclassification bias) is unknown.

This paper therefore showed that it was possible to estimate transition point from routinely collected healthcare data and that doing so could potentially offer advantages over use of a simple age cut-off, enabling better research into transition with large, representative datasets.

9.4 Paper 4: Adult healthcare is associated with more emergency healthcare for young people with life-limiting conditions (objective 4)

The development of a technique for estimating transition point from routinely collected hospital records (paper 3, above) opened up the opportunity to use these data to better answer the question of whether there are changes in healthcare use at the transition to adult care for young people with life-limiting conditions in England.

It was recognised, and highlighted in discussions with the Family Advisory Board, that there are other transitions taking place around the same ages as the healthcare transition. There may be transitions in education and transitions in access to benefits and associated support. For young people able to live independently without close support, there may be transitions between households (for example when moving for study or employment). For those requiring more support, there may be transitions between residential settings. Changes in healthcare use may also be linked to changes in risk taking behaviours (Finkelstein et al., 2017, Sawyer et al., 2007). I decided to compare young people with life-limiting conditions with those with no long-term condition for this reason: any changes in healthcare use not related to the healthcare transition should also be apparent in this comparator population.

There are also questions around what a ‘good’ transition should look like (recognising this might differ for young people, families and health service providers) and what effect this might have on

healthcare use. I decided to compare young people with life-limiting conditions to a second group (young people with diabetes) for whom transition has long been established and there is extensive research on transition processes (NHS England Medical Directorate, 2016, Kontopantelis et al., 2013). This second comparator group provided an indication of what change in healthcare use might be expected for a well-managed healthcare transition.

The fourth paper (Jarvis et al., 2022b) looks at changes in emergency hospital visits (emergency inpatient admissions and A&E visits) in England associated with being in adult care compared to being in paediatric care. It focused on these outcomes as two that may be expected to be linked to a worsening of care at transition and that can be seen as largely negative. While A&E visits and emergency inpatient admissions can be necessary, they are disruptive and traumatic events (Compas et al., 2012, Findlay et al., 2008, Franck et al., 2015, Commodari, 2010, DiFazio and Vessey, 2013, Wray et al., 2011, Clark et al., 2017) and there is no clear reason why they should increase at transition under optimal care. This is in contrast, for example, to other healthcare outcomes, such as GP consultations or outpatient appointments, for which an increase at transition could be reflective of additional support rather than additional problems. Changes for the young people with life-limiting conditions were compared to those for young people with diabetes or no long-term conditions, to provide comparisons with, respectively, a group experiencing only meaningful non-healthcare transitions and a group with a more established transition pathway from paediatric to adult healthcare.

After extensive consideration and discussion with supervisors and the Thesis Advisory Panel, I decided to analyse these data on a yearly basis (with random intercept models due to clustering within individuals across years) rather than another method such as interrupted time series. This was due to the difficulty in accounting for multiple time variables in an interrupted time series model - age of individual, time since transition and calendar year are all potentially relevant, to account for disease progression, short and longer term effects of transition and changes in service provision respectively. I now appreciate that it would be possible to include multiple variables in this way.

The study found evidence for increases in both emergency inpatient admissions and A&E visits in adult care, compared to paediatric care, in common with some previous studies (Blinder et al., 2013, Young et al., 2014, Young et al., 2007, Young et al., 2011, Wijlaars et al., 2018). However, unlike previous studies, comparison groups were included and increases in emergency hospital visits were found only for the life-limiting conditions group. The transition was not associated with changes in these events in the other groups. While no causal link was proven, some other explanations, such as

non-healthcare transitions at similar ages, seem less likely given the lack of changes in the comparison groups. A possible alternative explanation would be an acceleration of disease progression in the life-limiting conditions group coincident, but not due to, transition. Age was included in the model, so relationships between disease progression (with age as proxy) and the outcomes would be accounted for as long as they could be fitted well with the log link. Poor fitting could lead to changes in outcomes instead being wrongly linked to the transition variable. There are, however, reasons to believe that this is unlikely to have happened on a scale that would greatly change the results. For the association with transition to be, in fact, due to disease progression would require a consistent acceleration in disease progression (or, at least, numbers of emergency hospital care events) at ages coinciding with transition so that there were more events after transition than could be explained based on age. Estimated transition took place at a range of ages while any age-based acceleration in deterioration of condition would be expected to take place more consistently (at least, there is no reason to expect it to be correlated with transition age). There is no clear reason to expect any acceleration in emergency hospital care to happen more after transition than before transition. Nonetheless, it would be useful, in a large dataset, to explore associations of emergency hospital care events with transitions across some of the more common life-limiting conditions with well understood disease progression to check whether results differed between those know to have acceleration in deterioration during transition years with those known to have such acceleration either before or after transition ages. This is the first paper to assess changes in healthcare for young people with life-limiting conditions transitioning to adult healthcare using a large, representative dataset without assigning transition status based on age.

9.5 Paper 5: GPs' role in caring for children and young people with life-limiting conditions: a retrospective cohort study (Objective 5)

Discussion with parents and reports of limitations of primary care in the literature (Care Quality Commission, 2014, Mitchell et al., 2016, Neilson et al., 2015) raised the question of what good GP care would look like for young people with life-limiting conditions and whether this might be associated with reduced use of emergency hospital care. Discussions with parents helped to clarify this from their perspective, with parents raising a lack of regular GP contact and inconsistency in GP seen as frustrations and potential barriers to the most effective care.

The fifth paper (Jarvis et al., 2020) focuses on these two aspects of GP care, defining measures of regularity of GP contact (coefficient of variation: standard deviation of length of gaps between face to face GP appointments divided by mean gap (Johnson and Welch, 1940)) and consistency in GP seen (usual provider of care index - proportion of face to face appointments with most commonly

seen GP (Barker et al., 2017)). Only appointments recorded as face to face were included due to ambiguity around the meaning of other recorded events - e.g. which other events were clinical and which were administrative. However, there are also issues around the nature of face-face appointments, for example the role of the staff member involved - it may be that some young people would have both regular appointments with one GP and with one or multiple nurses. My research found that, in England, less regularity in GP consultations was associated with higher numbers of emergency inpatient admissions and A&E visits and that greater consistency of GP seen was associated with lower numbers of A&E visits.

These findings are consistent with ideas that a lack of familiarity with a GP may lead to increased A&E visits, bypassing primary care (Barker et al., 2017, Care Quality Commission, 2014, Lemer, 2013). They are also consistent with research from the United States linking attendance at 'well child' checks to reduced hospital admissions (Shumskiy et al., 2018). The paper did not specifically look at pre- and post-transition populations due to limitations in sample size when also assessing associations with ethnic group and condition category. It does show that irregular contact and lack of consistency in GP seen is associated with more emergency hospital care. This ties in with other research indicating the importance of consistent and accessible primary care (Pereira Gray et al., 2018, Palmer et al., 2018).

10 Discussion

10.1 Summary and contributions to the field

Overall, my research shows:

- that the population of young people with life-limiting conditions in England reaching ages at which transition to adult healthcare takes place is growing rapidly and becoming more complex in terms of different specialties of care and numbers of comorbidities
- there is international evidence for an increase in emergency department visits associated with the transition to adult healthcare in this population
- that there is an increase in emergency hospital care associated with the transition to adult healthcare for this population in England
- that consistent and regular GP contact is associated with reduced emergency hospital care in England.

I have also developed methods that will aid future research in estimating transition point and assessing medical complexity from routinely collected healthcare data.

My research has increased understanding of the population of young people with life-limiting conditions reaching the ages at which transition to adult healthcare is expected to take place. It provides the first estimation the size of this group, with life-limiting conditions diagnosed in childhood and surviving to adulthood. It also provides the first assessment of medical complexity in this population and operationalises concepts of medical complexity in routinely collected hospital records.

I, for the first time, reviewed systematically the evidence for changes in healthcare use across the whole population with life-limiting conditions, rather than focusing on a few of the more specific conditions. I found evidence for increases in Emergency Department use after transition to adult healthcare and also showed the lack of research using larger representative datasets without being limited by using a simple age cut-off to assign transition status.

I developed a method for estimating the point of transition from paediatric to adult healthcare from routinely collected hospital records, overcoming limitations of previous research in this area, compared it to other methods and showed, through simulation, its potential to increase sensitivity by reducing misclassification bias.

I used the developed methods to undertake the first analysis of changes in emergency healthcare associated with transition in this population that used a large, nationally representative dataset without relying on a simple age cut-off to assign transition status. The use of comparison groups provides greater confidence that observed changes are not simply associated with other transitions and events happening at similar ages to the healthcare transition.

Finally, I demonstrated that what parents have suggested they see as good primary care - regular access to the same GP - is associated with reduced emergency hospital care for young people with life-limiting conditions.

The methods I have developed have applicability, not only for future studies on young people with life-limiting conditions, but on assessing transition to adult care and for assessments of medical complexity in wider populations with chronic conditions.

10.2 Strengths and limitations

There are a number of strengths to my PhD research, but also limitations related to data, data availability and the time limitations inherent in doctoral research. These are considered in detail in the papers, but some broad areas applicable across studies are set out below.

10.2.1 Routine healthcare data

This research makes use of routinely collected healthcare data from England, providing national, representative time series data. Other countries, particularly those with single-payer healthcare services, have healthcare data that may be used for research. However, England has one of the largest datasets, with consistent data collection across NHS hospitals. This is useful when studying small sub-populations with rare conditions.

Routinely collected healthcare data have had limited use in this population, with (as illustrated in my systematic review) many studies focusing instead on single-clinic samples. This may be due to barriers in data access (for good reasons of data protection and governance) and in the skills required to analyse such data, with a need for quality control and linkage of multiple, large datasets requiring specialist software such as statistical packages and, often, databases. Small samples of data from a single clinic may be easier to obtain (particularly for clinical staff who already have access to the data for other purposes) and may be richer in detail (e.g. including full written notes) than national routinely collected data. However, as described above, they may lack generalisability to the wider population.

The available routine data do, also, have limitations. The HES data lack information on presence, other than that which is inferred through interactions with hospital services. If a young person has no interaction with a hospital in a year then that person is absent from HES data in that year - they could be present in the population, have migrated (including to another of the UK nations) or have died. While the last can be determined from linked Office for National Statistics Death Registration data, for individuals not known to have died, it is impossible - in the absence of presence in the data - to know whether they were still alive and resident in England. This has implications for estimates of prevalence (as those without hospital interactions may not be counted). It also affects estimates of complexity as the known population is limited to those with hospital interactions and so skewed towards those with greater medical complexity. This may not be a major problem for the population with life-limiting conditions - outpatient appointments (at least) might be expected - but may be a greater issue for other chronic conditions. HES data also, being hospital only, give no insights on primary care. They are also limited in diagnostic information, using the International Classification of Diseases 10th Edition system, which can lack specificity for some diagnoses (e.g. all types of muscular dystrophy share a single diagnostic code). When attempting to identify a population of interest from diagnostic codes, this lack of specificity may lead to an imperfect sample, including - for example - some individuals that do not truly have life-limiting conditions.

The Clinical Practice Research Datalink overcomes some of these issues and was selected for three of the secondary data analysis papers presented. Primary care data, including dates of registration with a GP, solve the problem of determining presence - if a person is registered with a GP in England then they are counted as present. However, CPRD data come with their own limitations. Although broadly nationally representative, CPRD GOLD is geographically skewed as noted above. There can be issues with limited follow-up - if a person moves from one GP practice to another (even if both GP practices contribute data to CPRD GOLD) then they cannot be identified as the same person. This introduces possible issues of representativeness if, for example, those in more deprived areas move more often (Cohen et al., 2013) they may be more likely to be lost to follow-up. There is also a possibility of double counting: if someone moves from one included practice to another they appear as two distinct people. These issues have particular relevance to paper 5, in which it should be acknowledged that there are regional variations in the outcomes considered, particularly A&E attendances, and also potential for regional variations in the variables of interest (particularly usual provider of care index if practice sizes vary). It cannot be discounted that some of the observed variation may be due to these issues. As previously noted, CPRD Aurum provides larger (and different) geographical coverage and could be an interesting comparison dataset. Inclusion of mean counts of A&E visits in the general population of the same age within the same region would also be a potential control for this variation.

Demographic data are also limited in CPRD data: ethnic group comes only from linked HES data and so is only available for those having interactions with hospital services and deprivation category is based on the last known address only. The latter, in particular, makes it impossible to study any trajectories in deprivation - if someone moves location, even if they stay registered with the same GP, previous data on deprivation is lost. HES data provided linked to CPRD data is also less rich than HES data from NHS Digital, with some data fields deliberately omitted or limited to prevent linkage with other HES extracts (for example, full HES can contain Lower Super Output Area of residence, useful for applying alternative or population weighted deprivation measures; these data are not available in CPRD HES data). The largest problem, however, with CPRD GOLD data for the analyses presented here is sample size. Although a large sample (approximately 8% of the England population) when studying relatively rare conditions, there are challenges around statistical power and limited ability to study sub-groups of conditions or ethnic groups. In the presented studies, choices had to be made between comparisons of age groups (or transition status) and comparisons between ethnic groups or condition categories; in national HES data, the study population can be large enough to consider all of these together. Finally, data management in CPRD is more challenging than in HES, particularly when linking with HES (see Appendix 3: Data analysis plan for

CPRD data (papers 3 and 4), page 288, for more detail on the data management required), increasing analysis complexity and the risk of errors.

The proposed new NHS Digital dataset for primary care potentially addresses many of these issues, promising full population primary care data that is readily linked with full HES data (de Zulueta, 2021). Availability of such data for the present research would have enabled analysis of sub-groups of conditions not possible in the papers using CPRD data and, potentially, simplified analysis depending on the ease of linking data.

Finally, children's hospices can be an important part of care for this population and can be involved in care for many years (Taylor et al., 2010), but these interactions are not captured in any available routine data. It is not possible to determine from HES or CPRD data whether a young person has contact with a hospice at all (there may be some instances where admission or discharge is from or to a hospice, but this fails to capture other individuals receiving hospice support). The data - and my research papers - are therefore silent on the role of hospices in transition.

10.2.2 Patient and public involvement

The Martin House Research Centre, shortly before the start of this research, developed a Family Advisory Board composed of parents or former parents of children with life-limiting conditions (Martin House Research Centre, 2019). Meeting regularly, issues can be raised with the FAB at short notice and feedback sought. This proved invaluable for my research as highlighted above. A limitation was that feedback was sought primarily from carers, rather than from the young people themselves. The latter is more challenging, due to issues around capacity of some young people with life-limiting conditions to take part in such discussions, limited experience among many of them of transition to adult healthcare and practical issues around arranging meetings around treatment, education etc. (Mitchell et al., 2019). During my doctoral research, the Centre has nonetheless begun to involve young people themselves more in PPI for future research. I look forward to working with this group in the future.

10.2.3 Breadth and focus

A strength of my research, given many pre-existing studies focused on individual clinics and individual conditions, has been looking widely across life-limiting conditions and making use of nationally representative data. This has enabled rare conditions to be included in analyses. There are also limitations in treating a population as diverse as that of young people with life-limiting conditions as a single group. Not all experiences are the same and transition may have different effects by condition, demographics and geographic region, particularly when services differ. These

can however be addressed in future studies, making use of the techniques I have developed and future, more comprehensive, primary care data.

10.3 Implications for young people and their families

The findings from this research reinforce the views held by young people and their families that there are problems with the transition to adult healthcare and that these may be linked to increased use of emergency hospital care. The research on GP contact suggests that regular consultation with a GP, particularly the same GP, is associated with reductions in emergency hospital care. Development of the relationship between GP, family and young person, increasing understanding and knowledge, may provide benefits for young people and their families in providing a more local and potentially less distressing setting for receipt of care and advice. However, there are limitations to the role of the GP for this population, given current practices around out of hours working and home visits (Kenway and Palmer, 2007).

There is little that young people and their families can directly change. The lack of change in emergency hospital care use for young people with diabetes does suggest that a transition to adult healthcare with limited impact is possible. This, however, remains mainly the responsibility of policymakers, commissioners and service providers.

10.4 Implications for healthcare providers and policy makers

The research adds to existing evidence of in increases in emergency hospital care use after transition (Wijlaars et al., 2018). It shows that the population of young people with life-limiting conditions reaching transition ages is growing rapidly, with increasing complexity in terms of numbers of comorbidities and numbers of different main specialties of consultants involved in care. Healthcare providers face increases in the numbers of young people with life-limiting conditions going through transition, the complexity of that transition (with different care teams involved) and increasing demand on healthcare services, particularly emergency healthcare services, after transition.

There are some suggestions, from the present research, from the literature and from recent policy developments on how improvements may be achieved. The present research suggests that diabetes services handle the transition with minimal impacts on emergency care use. While people with diabetes are a very different population without necessarily progressive needs and lower routine healthcare needs, there may be lessons to be learned (NHS England Medical Directorate, 2016). My systematic review revealed differences in evidence for healthcare use post- compared to pre-transition in different countries. For example, most studies from Canada showed increases in outpatient attendances and decreases in inpatient admissions post-transition, while most studies from the United States showed the reverse (Jarvis et al., 2021b). This may be due to different

payment systems in those countries, with adolescents with special health care needs in the United States having higher risk than the general population of losing public health insurance on reaching adulthood (Okumura et al., 2007), which could explain reductions in outpatient attendance. Lower utilisation of outpatient healthcare services has also been linked to high inpatient use in the United States (Ozturk et al., 2014). It is likely that healthcare needs in the population with life-limiting conditions do not decrease after transition (with progressive conditions, they are likely to increase) and so must be met either through a combination of primary and outpatient care or, if this is lacking, are likely to be met through emergency care. Providing good routine care that meets needs should be a priority.

The NHS long term plan sets out a vision of "selectively moving to a 0-25 years service" (NHS England, 2019). While there is a risk that this merely moves the problem of transition, there are many arguments in its favour. At present, an exemplar of transition begins with planning and consultation by around 14 years, when the young person is still a child (National Institute for Health and Care Excellence, 2016). As such, while there are aims to involve children *and* parents in the decision making, parents are still the primary decision makers during this process and so there is a danger that the child's wishes are not fully heard (Azzopardi et al., 2016, Bensen et al., 2015, Coyne et al., 2017, Coyne et al., 2016, Fegran et al., 2014). Transitioning during adulthood would potentially give those young people with life-limiting conditions more agency (if they have capacity) in the nature of their on-going care. A transition at age 25 years would also avoid other transitions currently taking place around the same time as the healthcare transitions, such as in education and residential settings and, potentially, in employment and independence in other areas of life. Finally, delaying transition until 25 years would enable those who are unlikely to survive to that age to avoid transition altogether - a significant proportion of deaths still occur from 16-25 years (Gibson-Smith et al., 2020).

Even without a formal healthcare transition, there will be many changes as a young person reaches adulthood. For those with capacity, ultimate decision making over care and consent to treatment passes from parents to the young person and - as noted above - there are a number of other potential transitions. Moving to residential care away from the family home that may necessitate changes in healthcare providers for geographical reasons. However, for young people staying in the family home and particularly for those lacking capacity, transition and its problems might be eliminated or at least substantially delayed and able to take place at a time when there are fewer contemporaneous changes.

The role and remit of children's hospices should also be considered. There is a lack of available research data from these organisations, which prevented my research from considering their role. Children's hospices differ from each other in the maximum age to which they offer services and the services they provide to young adults, although some provide services to young people aged up to 26 years (Knighting et al., 2018). As such, some children's hospices offer a degree of continuity of support during the transition from paediatric to adult healthcare in the NHS. Careful consideration should be given to whether age limits for children's hospice support should be aligned with NHS services transition, particularly if the NHS moves to a 0-25 years service.

It is important that the views of young people and their families are considered and services are designed around their needs and desires. There should be flexibility in transition depending on individual circumstances and prognosis - some young people may wish to change to more age appropriate services prior to 25 years and it should be recognised that transition is not always negative (Sheehan et al., 2015, Fegran et al., 2014). Services continuing to 25 years can no longer be seen as purely paediatric or treat young people as children when they are adults.

10.5 Implications for research and future research priorities

My research identifies a number of implications for research and priorities for future investigation.

My analysis of the numbers and medical complexity of young people with life-limiting conditions reaching transition ages underlines the importance of this group for study. The group is growing markedly and shows greater complexity in numbers of conditions and numbers of consultants with different main specialties overseeing care, but limited evidence for increasing healthcare use overall. It is important, in designing the best services for this population - including unified services up to 25 years as outlined above - to understand variations within the healthcare needs of this population. The analyses I have conducted may mask variations within this group - with some conditions, for example, being associated with an increased period of greater stability and lower hospital healthcare use along with greater survival times, while others may have a longer period of instability and greater healthcare use. Understanding these possible variations and size and growth rate of these populations will be essential for planning good services and should be a research priority.

The systematic review showed conflicting evidence, with many different measures and common limitations in studies either having small, potentially unrepresentative samples or large samples relying on a simple age cut-off to assign transition. My work on estimation of transition age shows that a simple age cut off misclassifies many individuals and has the potential to lead to significant underestimation of differences between pre- and post-transition care. Given the ability to estimate transition point from routine data (by my methods or others) it is important that future research

should, where possible, seek to use nationally representative data and estimate transition point from the data in the absence of explicit information on transition. As noted above, there is now a need to explore the trends in population size and healthcare use of those with different conditions as they approach transition. For the less common conditions, this is most realistically done with large scale routinely collected data.

My secondary data analysis on healthcare use changes associated with the transition focused on emergency hospital care, due to this being highlighted in earlier studies and by the Family Advisory Board as an aspect of care expected to be impacted by transition. However, this does not give the full picture. My research on the role of the GP in caring for young people with life-limiting conditions shows an association between GP contact and emergency healthcare. It would be useful to explore this further, specifically within the population undergoing transition, to see whether there is an association between pre-transition GP contact and post-transition changes in emergency care use. My systematic review also showed different patterns between post-transition outpatient attendance and post-transition inpatient admissions in Canada and the United States; it would also be useful to investigate any association between outpatient and inpatient care in England after transition. This research would help to highlight potential areas in which investment might be made to mitigate negative effects of transition.

Qualitative research also has an important role in this population, to better understand the reasons for increases in emergency healthcare use after transition and to potentially highlight good practice that might reduce this. While there are qualitative studies looking at transition experiences, there is potential for more focused studies looking at particular aspects, for example experiences of primary care from the perspective of both clinicians and service users.

Many changes to transition services have been proposed, from best-practice guidelines to the use of transition clinics or specialist adolescent services. These should be rigorously evaluated and should incorporate economic analyses to identify service models that provide best value for money. While it is challenging in this population to evaluate benefits to service users, the development of outcome measures will enable better comparisons.

Finally, it is important that proposed 0-25 years services should be rigorously evaluated if introduced. Changes in NHS services are too often left unevaluated and it is important to establish the benefits (if present) of such services given that they may cost more than current services. It will also be important to understand whether there are groups for whom a 0-25 service may not be desirable, to understand whether 25 years is an appropriate target age to transition to standard adult services and to take account of different experiences and needs. Children's hospices (and adult

hospices) will also need to consider the age ranges they wish to and are able to support and how this aligns with any reorganisation of NHS services. This too, points towards a need for a mix of qualitative and quantitative studies.

11 Conclusions

There is an increase in emergency hospital care for young people with life-limiting conditions associated with the transition to adult healthcare. The population of young people with life-limiting conditions transitioning to adult healthcare is growing rapidly and becoming more complex with more comorbidities and consultants of more different specialities involved in their care. This makes managing transition well for this population both more challenging, due to the numbers of healthcare teams involved, and more important than ever due to the increasing numbers reaching transition.

Regular contact with the same GP is associated with reduced use of emergency healthcare and the role of the GP should be considered as part of any reforms to improve experiences of transition to adult care and of adult healthcare itself.

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Appendix 1: Published papers

The published papers comprising this thesis are reproduced in the following pages. Supplementary materials for each paper, if applicable, are to be found in Appendix 2: Supplementary materials for the papers, beginning on page 124. For each paper, information is given on where in the appendix to find any supplementary materials referenced in the paper.

A1.1 Paper 1: Numbers, characteristics, and medical complexity of children with life-limiting conditions reaching age of transition to adult care in England: a repeated cross-sectional study

Full citation: Jarvis, S., Richardson, G., Flemming, K. and Fraser, L., 2022. Numbers, characteristics, and medical complexity of children with life-limiting conditions reaching age of transition to adult care in England: a repeated cross-sectional study. *NIHR Open Research*, 2, p.27.

The published paper is reproduced in the following pages.

There are no supplementary materials for this paper.

Please see Section 9.1 for discussion of other relevant issues identified since publication of this paper.

RESEARCH ARTICLE

Numbers, characteristics, and medical complexity of children with life-limiting conditions reaching age of transition to adult care in England: a repeated cross-sectional study [version 1; peer review: 1 approved]

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Abstract

Background: The number of children with life-limiting conditions in England is known to be increasing, which has been attributed in part to increased survival times. Consequently, more of these young people will reach ages at which they start transitioning to adult healthcare (14-19 years). However, no research exists that quantifies the number of young people with life-limiting conditions in England reaching transition ages or their medical complexity, both essential data for good service planning.
Methods: National hospital data in England (Hospital Episode Statistics) from NHS Digital were used to identify the number of young people aged 14-19 years from 2012/13 to 2018/19 with life-limiting conditions diagnosed in childhood. The data were assessed for indicators of medical complexity: number of conditions, number of main specialties of consultants involved, number of hospital admissions and Accident & Emergency Department visits, length of stay, bed days and technology dependence (gastrostomies, tracheostomies). Overlap between measures of complexity was assessed.
Results: The number of young people with life-limiting conditions has increased rapidly over the study period, from 20363 in 2012/13 to 34307 in 2018/19. There was evidence for increased complexity regarding the number of conditions and number of distinct main specialties of consultants involved in care, but limited evidence of increases in average healthcare use per person or increased technology dependence. The increasing size of the group meant that healthcare use increased overall. There was limited overlap between measures of medical complexity.
Conclusions: The number of young people with life-limiting

Open Peer Review

Approval Status ✓

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version 1 08 Apr 2022	✓ view

1. **Intira Jeannie Collins**, University College London, London, UK

Any reports and responses or comments on the article can be found at the end of the article.

conditions reaching ages at which transition to adult healthcare should take place is increasing rapidly. Healthcare providers will need to allocate resources to deal with increasing healthcare demands and greater complexity. The transition to adult healthcare must be managed well to limit impacts on healthcare resource use and improve experiences for young people and their families.

Keywords
Life-limiting conditions, Transition to adult care, Medical complexity, Healthcare use, Palliative care

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Author roles: Jarvis S: Conceptualization, Data Curation, Formal Analysis, Funding Acquisition, Investigation, Methodology, Project Administration, Software, Validation, Visualization, Writing – Original Draft Preparation, Writing – Review & Editing; **Richardson G**: Conceptualization, Methodology, Supervision, Validation, Writing – Review & Editing; **Flemming K**: Conceptualization, Methodology, Supervision, Writing – Review & Editing; **Fraser LK**: Conceptualization, Funding Acquisition, Methodology, Supervision, Validation, Writing – Review & Editing

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Plain english summary

Life-limiting conditions are conditions that shorten or threaten to shorten life. Children with these conditions receive healthcare from specialist children's services. As adults, they get treated in adult services, often overseen by a General Practitioner (GP). The transition often happens between 14 and 19 years.

Healthcare providers need information on these young people to provide good services. We don't know much about how many there are, what conditions they have, whether they are male or female, what ethnic group they are in or where they live. We also don't know whether their healthcare needs are becoming more complex.

We aimed to discover how many of the children survive into adulthood. We also wanted to know the number of people from different ethnic groups, regions, areas of high or low deprivation and how many were male and female. We looked at how complicated healthcare needs were by counting how many long-term conditions they had and how many different care teams were involved. We also counted admissions to hospital and visits to Accident & Emergency (A&E) Departments and how many needed technology to help with eating or breathing. This was all done using records routinely collected by the NHS.

The number of young people with life-limiting conditions surviving to adulthood had increased. There were 20363 in 2012/13 and 34307 in 2018/19. The number from minority ethnic groups had increased, particularly the Mixed and Pakistani groups. The young people had more long-term conditions as time went on. They also had more different medical teams involved in care. They had more visits to A&E Departments. Admissions to hospitals per person had not increased.

Healthcare providers need to be aware of these changes. Increasing numbers make it more important to get transition right. Increasing numbers of conditions and medical teams involved make this more difficult.

Introduction

The number of children with life-limiting conditions in England has increased over the past two decades[1,2]. These conditions often involve medical complexity and include conditions that inevitably lead to premature death and also life-threatening conditions that may result in premature death, but may also be cured (e.g. cancer)[3].

These increases in prevalence of life-limiting conditions have been attributed, at least in part, to increased survival[1,2,4,5]. A consequence of this is the expectation that more children with life-limiting conditions will survive long enough to transition from paediatric to adult healthcare, something that typically happens from 14 to 19 years in the UK[6–8]. The transition - and associated problems - have been an area of increasing research and policy interest, with variations in experience identified between conditions and availability and remit of local services[7,9–13]. Providing good transition care is important for efficient use of health services and reducing emotional trauma for young people and their families[14–19].

Concepts of medical complexity, indicative of the need for 'extra time, expertise, and resources necessary to achieve optimal health outcomes'[20], have been used as a tool to identify young people, with life-limiting or other chronic conditions, who have extensive healthcare needs[20–23]. These children have been shown to be major users of healthcare across multiple specialties[24,25] and the related group of children with disabilities has been shown to also have complex care needs and healthcare use correlating with complexity[23].

High healthcare use across multiple specialties associated with medical complexity, coupled with the acknowledged challenges in transitioning children with life-limiting conditions into adult care, presents challenges for service providers. There is a need, for good service planning, for knowledge on how many young people with life-limiting conditions are at ages where transition to adult care should take place, whether their characteristics (such as category of health condition or ethnic group) are changing over time and how complex their medical needs are.

While previous studies have estimated the numbers of young people with life-limiting conditions, including within age groups close to transition ages[1,2], these studies have not differentiated between those with conditions diagnosed in childhood (and therefore likely to undergo transition) and those with conditions diagnosed in late adolescence (who may go directly into adult care). There are no studies assessing the medical complexity of this population on a national basis in England.

This study uses routinely collected hospital records to assess national trends in the numbers, characteristics, and medical-complexity of young people with life-limiting conditions reaching the age to transition to adult healthcare in England.

Methods

Ethical approval

Health Research Authority ethical approval was obtained for this study from Wales Research Ethics Committee 5 (REC reference 20/WA/0149, chair Dr Jason Donal Walker, Integrated Research Application System project ID 282131).

Patient and public involvement

The Martin House Research Centre Family Advisory Board[26], which comprises parents and carers who either have or had children with life-limiting conditions, was consulted about the challenges of transition and the complexity of healthcare in this population. Their input helped to determine the aspects of healthcare assessed in this study.

Data

Hospital Episode Statistics (HES) (records of hospital care in England funded by the National Health Service (NHS)[27]) data were requested from NHS Digital. Inpatient

(1 April 2006 - 31 March 2019), outpatient (1 April 2006 - 31 March 2019) and Accident & Emergency (A&E, 1 April 2007 - 31 March 2019) were requested for all children and young people aged 12–23 years at any point between 1 April 2007 - 31 March 2019.

Data management

Data were managed in Microsoft SQL Server 2019. Other SQL servers such as MariaDB (MariaDB, RRID:SCR_021763) or MySQL can also be used. Analyses and graphs were produced using R project version 3.5.3 (R Project for Statistical Computing, RRID:SCR_001905).

Population of interest. This was a repeated cross-sectional study. In each year, individuals were included if they met the following criteria:

- Had a diagnosis of a life-limiting condition in HES inpatient or outpatient records, matching a previously developed[1] International Classification of Diseases, 10th Edition[28] (ICD-10) coding framework in that year or a previous year while aged 16 years or younger. Perinatal diagnoses from the framework were excluded as, without subsequent life-limiting diagnoses in another category, they were not deemed indicative of an ongoing life-limiting condition at transition ages (Table 1).
- Had a HES record in the year while aged 14–19 years and was a resident in England.

Individuals were excluded in a year if they:

- Had only a non-central nervous system cancer life-limiting condition diagnosis (see Table 1) and were first diagnosed more than five years earlier (those having another life-limiting condition diagnosis were not excluded). The rationale for this was that few young people with a non-central nervous system cancer diagnosis more than five years earlier would still be considered life-limited[1].

Demographic data. Age for each person in each year was set to the age of the first record (inpatient, outpatient, or A&E) for that person in each year. Sex was assigned as the most commonly recorded sex in the data. Ethnic group was recorded in the data based on 2001 census groups[29]. These were collapsed to eight groups (White, Indian, Bangladeshi, Pakistani, Black, Chinese, Mixed and Other) to avoid small numbers and then each person was assigned to the most commonly recorded group. Government Office Region of residence was assigned according to the first non-missing value recorded in each year. In the event of no non-missing values in a year, the value from the nearest previous year with a non-missing value was used. Deprivation category was assigned based on the first non-missing Lower Super Output Area (LSOA - a geographic area of, on average, 1500 residents, although sizes vary) of residence recorded in each year - deprivation categories were assigned by population weighting so that approximately 20% of 14–19-year-olds in the general population were in each group. In the event of no non-missing LSOA values in a year, the value from the nearest previous year with a non-missing value was used.

Study period. Data from 1 April 2006 to 31 March 2019 were used to determine inclusion eligibility (i.e., analysed for presence

Table 1. Coding framework for life-limiting conditions.

Diagnostic Group	ICD-10 diagnostic codes
Neurology	A17 A810 A811 F803 F842 G10 G111 G113 G12 G20 G230 G238 G318 G319 G35 G404 G405 G600 G601 G702 G709 G710 G711 G712 G713 G800 G808 G823 G824 G825 G934 G936 G937
Haematology	B20 B21 B22 B23 B24 D561 D610 D619 D70 D761 D81 D821 D83 D891
Oncology	C D444 D48 (Central Nervous System: C70, C71, C72, D33, D43)
Metabolic	E310 E348 E702 E71 E72 E74 E75 E76 E77 E791 E830 E880 E881
Respiratory	E84 J841 J96 J984
Circulatory	I21 I270 I42 I613 I81
Gastrointestinal	K550 K559 K72 K74 K765 K868
Genitourinary	N17 N184 N185 N19 N258
Congenital	Q000 Q01 Q031 Q039 Q040 Q042 Q043 Q044 Q046 Q049 Q070 Q200 Q203 Q204 Q206 Q208 Q213 Q232 Q218 Q220 Q221 Q224 Q225 Q226 Q230 Q234 Q239 Q254 Q256 Q262 Q264 Q268 Q282 Q321 Q336 Q396 Q410 Q419 Q437 Q442 Q445 Q447 Q601 Q606 Q614 Q619 Q642 Q743 Q748 Q750 Q772 Q773 Q774 Q780 Q785 Q792 Q793 Q804 Q81 Q821 Q824 Q858 Q860 Q870 Q871 Q872 Q878 Q91 Q920 Q921 Q924 Q927 Q928 Q932 Q933 Q934 Q935 Q938 Q952
Other	H111 H498 H355 M313 M321 M895 T860 T862 Z515

ICD-10 diagnostic codes were used to identify life-limiting conditions in this study. Where codes shorter than four digits are quoted, all four-digit sub-codes are included. ICD-10: International Classification of Diseases, 10th Edition.

of life-limiting conditions and other diagnoses). However, only data from 1 April 2012 to 31 March 2019 are presented, due to left-edge effects, ensuring that all included individuals had at least three years of data aged 16 years or younger in which a life-limiting condition - and eligibility for inclusion - could be detected (Figure 1).

Numbers and characteristics of young people of transition age. Numbers of young people aged 14–19 years and known to be present in England (i.e., with an inpatient, outpatient, or A&E record while a resident in England) were calculated each year, overall and by age, sex, ethnic group, Government Office Region of residence and deprivation category.

Medical complexity. Analyses of medical complexity drew on earlier work[20], matching concepts of complexity to the available data (Figure 2). While the data lack information on family identified needs or impacts on the family, the HES data do provide insights on the other three main concepts of presence of chronic conditions, healthcare use and functional limitations. These were measured as follows.

Chronic conditions

This aspect of complexity was assessed through the presence of life-limiting conditions, as described above, and also a measure of the number of distinct categories of conditions (including life-limiting and other chronic conditions) using previously developed[30] groupings for chronic conditions (Table 2 - explicitly perinatal diagnoses were again excluded as they were not relevant in a population aged 14–19 years). For distinct categories of chronic conditions, in each year for each person the total number of diagnostic categories recorded in inpatient and outpatient records in that, or previous years, was calculated.

Healthcare use - multiple service providers

The 'multiple service providers' aspect of complexity was assessed through the number of distinct consultant main specialties (MAINSPEF field in inpatient and outpatient datasets, as detailed in the Hospital Episode Statistics Technical Output Specification) recorded for each person in each year in the inpatient and outpatient data. Similar paediatric and adult specialties were considered a single specialty (Table 3) to prevent any variations in the numbers in paediatric or adult care from skewing results; all other unique specialty codes were considered distinct.

Healthcare use - high resource use

The 'high resource use' aspect of complexity was assessed through different measures of hospital events: total A&E visits, inpatient admissions, emergency admissions and inpatient bed days for each person in each year. Length of stay was also assessed in each year.

Functional limitations

Technology dependence was assessed through the numbers of young people with life-limiting conditions with a gastrostomy or tracheostomy present in each year. Insertion (permanent or temporary), attention to or removal of a gastrostomy or tracheostomy was considered evidence of presence in a given year. Permanent insertions were assumed to remain in later years until there was evidence of removal. Presence, insertion and removal of gastrostomies and tracheostomies were identified through ICD-10 diagnostic codes[28] and OPCS Classification of Interventions and Procedures Version 4 (OPCS-4) procedure codes recorded in the inpatient and outpatient data (Table 4).

Overlaps between measures of complexity

Finally, the interconnectedness of measures of complexity was assessed by using UpSet graphs, using the R package, UpSetR version 1.4.0. UpSet graphs are an alternative to Venn or Euler diagrams, which show sizes of intersections between many different sets[31]. Set sizes are shown with bar graphs to the left of set names, while a matrix shows

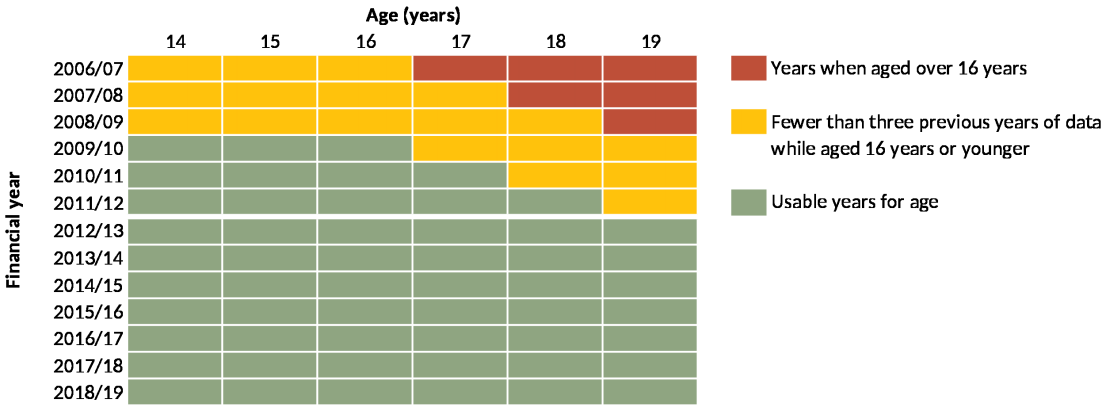

Figure 1. Years of data that could be used in the analysis. Years of available data showing the years in which, for each age in that year, there were data for at least three earlier years while a young person of that age was aged 16 years or younger.

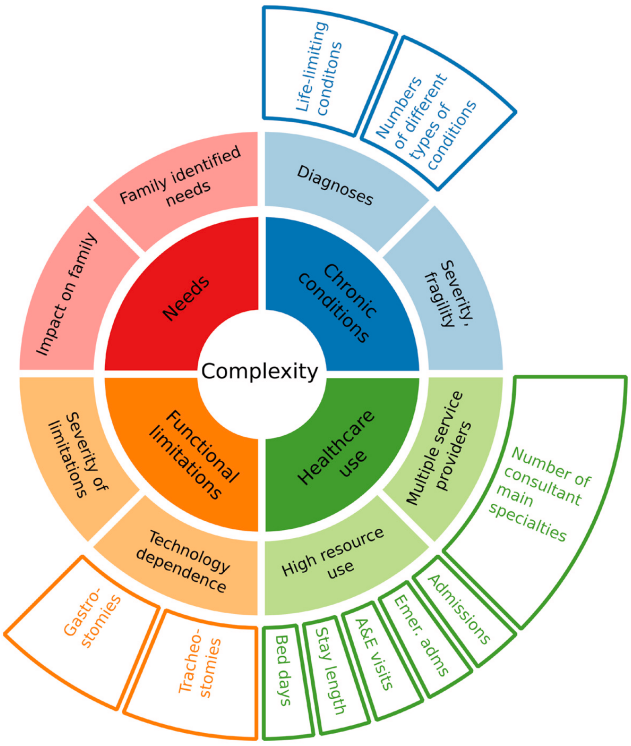

Figure 2. Conceptualisation of complexity and relevant data. Inner two rings, adapted from earlier work[20], show conceptualisation of complexity. Outer ring shows relevant measures in the data.

Table 2. Grouping of chronic conditions to count numbers of distinct chronic conditions.

Category	ICD-10 codes
Substance abuse	E244, F10-F19, F55, G240, G312, G405, G621, G720, G721, I426, K292, K70, K852, K853, K860, O354, R781-R785, Y47, Y49, Z502, Z503, Z714, Z715, Z722, Z864
Self-harm	X60-X84, Y10-Y34, Y870, Y872, Z915
Other mental health problems	F00-F01, F028, F03-F09, F20-F48, F50, F53, F54, F59, F60-F69, F99, Z093, Z504, Z865, Z914
Behavioural/ developmental disorders	F70-F79, F800-F802, F808, F809, F81-F84, F88, F89, F90-F98
Neoplasms	C00-C97, D00-D02, D05-D09, D12, D13, D141-D144, D15, D20, D32-D35, D37-D48, D630, E340, E883, G130, G131, G533, G550, G631, G731, G732, G941, M360, M361, M495, M820, M906, M907, N081, N161, Y431-Y433, Y842, Z08, Z510-Z512, Z541, Z542, Z85, Z860, Z923
Immunological disorders	D80-D84, G532, Q980
Anaemia and other blood disorders	D50, D560-D562, D564, D568, D569, D570-D572, D578, D58, D610, D619, D64, D66, D67, D680-D682, D684-D689, D69, D70-D76, M362-M364, M904, N082, Z862
HIV	B20-B24, F024, R75, Z21
Other chronic infections	A50, A81, B18, B371, B375, B376, B377, B381, B391, B401, B440, B447, B45, B46, B487, B500, B508, B510, B518, B528, B520, B55, B572-B575, B580, B59, B67, B69, B73, B74, B787, B90-B94, F021, K231, K931, M00, N330, P350-P352, P358, P359, P37
Asthma and chronic lower respiratory disease	J41-J47
Cystic fibrosis	E84, P75

Category	ICD-10 codes
Respiratory injuries	S17, S27, S28, T27, T914
Respiratory congenital anomalies	Q30-Q37, Q790
Other respiratory	G473, J60-J70, J80-J86, J961, J98, P27, Y556, Z430, Z930, Z942
Diabetes	E10-E14, G590, G632, I792, M142, N083, O24, Y423
Other endocrine	E00, E030, E031, E071, E220, E230, E25, E268, E291, E31, E341, E342, E345, E348, G132, G735, Y421
Metabolic	D55, E70-E72, E74-E78, E791-E799, E800-E803, E805, E807, E83, E85, E880, E881, E882, E888, E889, G736, L990, M144, M143, N163
Digestive	K20, K210, K22, K238, K25-K28, K290, K291, K293-K299, K31, K50-K52, K55, K57, K592, K630-K633, K66, K72-K76, K80-K83, K850, K851, K858, K859, K861-K869, K870, K90, M074, M075, M091, M092, T864, Z432-Z434, Z465, Z903, Z904, Z932-Z935
Renal/ genitourinary	D638, G638, G998, I688, M908, N084, N00-N05, N07, N11-N15, N160, N162, N164, N165, N168, N18, N19, N20-N23, N25, N26, N28, N29, N31, N32, N338, N35, N36, N391, N393, N394, N40-N42, N70-N74, N80-N82, N85, N86, N87, N88, P960, T824, T831, T832, T834-T839, T855, T861, Y602, Y612, Y622, Y841, Z49, Z936, Z940, Z992
Congenital anomalies of the digestive/ renal/ genitourinary system	Q380, Q383, Q384, Q386-Q388, Q39, Q402, Q403, Q408, Q409, Q41, Q42, Q431, Q433-Q437, Q439, Q44, Q45, Q500, Q51, Q520-Q522, Q524, Q540-Q543, Q548, Q549, Q550, Q555, Q56, Q601, Q602, Q604-Q606, Q61, Q620-Q626, Q628, Q630-Q632, Q638, Q639, Q64, Q792-Q795, Q878, Q891, Q892
Digestive/ renal/ genitourinary injuries	S36, S37, S38, S396, S397, T065, T28, T915
Other/ unspecific metabolic/ endocrine/ digestive/ renal/ genitourinary	E66, G633, G990, M145, N92, Z863, Z938
Musculoskeletal/ connective tissue	G551-G553, G635, G636, G737, J990, J991, L620, M05, M06, M070-M073, M076, M08, M098, M10-M13, M140, M146, M148, M30-M35, M40-M43, M45-M48, M50-M54, M60-M62, M638, M801-M809, M811-M819, M821, M828, M840-M842, M848, M849, M85, M863-M866, M89, M900, M91-M94, N085, Y454
Skeletal injuries/amputations	S13, S220-S222, S225, S23, S32, S33, S683, S684, S688, S77, S78, S87, S88, S97, S980, S982-S984, T02, T04, T05, T203, T207, T213, T217, T223, T227, T232, T233, T236, T237, T243, T247, T252, T253, T256, T257, T293, T297, T303, T307, T312-T319, T322-T329, T873-T876, T912 T918, T926, T931, T934, T936, T940, T941, T950, T951, T954, T958, T959, Y835, Z891, Z892, Z895-Z898, Z971
Chronic skin disorders	L10, L110, L118, L119, L12-L14, L28, L40-L45, L57, L581, L59, L87, L88, L90, L92, L95, L93, L985, M090, Q80, Q81, Q870-Q875, Q894
Musculoskeletal/ skin congenital anomalies	Q188, Q650-Q652, Q658, Q659, Q675, Q682, Q683-Q685, Q71-Q73, Q74, Q753-Q759, Q761-Q764, Q77, Q78, Q796, Q798, Q820-Q824, Q829, Q862, Q897-Q899
Epilepsy	F803, G400-G404, G406-G409, G41, R568, Y460-Y466
Cerebral palsy	G80-G83
Injuries of brain, nerves, eyes or ears	S05-S08, S12, S14, S24, S34, S44, S54, S64, S74, S84, S94, T060-T062, T26, T904, T905, T911, T913, T924
Chronic eye conditions	H051-H059, H133, H17, H18, H193, H198, H21, H26, H27, H280-H282, H31, H328, H33, H34, H35, H40, H420, H43, H44, H47, H540- H542, H544, T852, T853, Z442
Chronic ear conditions	H602, H652-H654, H661-H663, H690, H701, H731, H740-H743, H750, H80, H810, H814, H830, H832, H900, H903, H905, H906, H91, Z453
Congenital anomalies of neurological or sensory systems	Q00-Q07, Q104, Q107, Q11-Q12, Q130-Q134, Q138, Q139, Q14-Q16, Q750, Q751, Q85, Q860, Q861, Q868, Q90-Q93, Q952, Q953, Q97, Q99
Other neurological	F022, F023,G00-G09, G10-G12, G138, G14, G20-G23, G241-G249, G25-G30, G310-G311, G318, G319, G32-G37, G43-G46, G470-G472, G474-G479, G50-G52, G530, G531, G538, G54, G558, G56-G58, G598, G60, G61, G620, G622-G629, G64, G70, G71,G722-G729, G730, G733, G90-G93, G942, G948, G95, G96, G98, G991, G992, I60-I67, I680, I682, I69, I720, I725, T850, T851, Y467-Y468, Z982
Congenital heart disease	Q20-Q26, Q893
Other cardiovascular	I00-I28, I31-I39, I41, I420-I425, I427-I429, I430, I431, I432-I438, I441-I447, I451-I459, I46-I51, I528, I70-I71, I721-I724, I728, I729, I73-I77, I790, I791, I798, I81-I82, I98-I99, M036, N088, Q27, Q28, S26, T820-T823, T825-T829, T862, Y605, Y615, Y625, Y840, Z450, Z500, Z941, Z95
Non-specific chronic conditions	R62, R633, Z431, Z515, Z755, Z931, Z993

ICD-10 diagnostic codes for chronic conditions (including life-limiting conditions) grouped into categories for the purpose of counting numbers of distinct chronic conditions. ICD-10: International Classification of Diseases, 10th Edition; HIV: human immunodeficiency virus.

Table 3. Related paediatric and adult consultant main specialties.

Codes	Descriptions of specialties
141, 142, 149	Restorative Dentistry; Paediatric Dentistry; Surgical Dentistry
320, 321	Cardiology; Paediatric Cardiology
400, 421	Neurology; Paediatric Neurology
710, 711	Adult Mental Illness; Child and Adolescent Psychiatry

Consultant main specialties spanning paediatric and adult disciplines that were treated as a single specialty for the purposes of counting distinct consultant main specialties each year. Codes are from the Hospital Episode Statistics Technical Output Specification (https://digital.nhs.uk/data-and-information/data-tools-and-services/data-services/hospital-episode-statistics/hospital-episode-statistics-data-dictionary) for field 'MAINSPEF' in Admitted Patient Care and Outpatient datasets

Table 4. Codes used to identify presence of gastrostomies and tracheostomies.

Coding system	Code	Interpretation
ICD-10	Z430	Tracheostomy present and assumed to remain until evidence of removal
ICD-10	Z930	Tracheostomy present and assumed to remain until evidence of removal
OPCS-4	E421	Tracheostomy present and assumed to remain until evidence of removal
OPCS-4	E423	Temporary tracheostomy - counted as present in year, but not in subsequent years unless evidence of subsequent permanent tracheostomy
OPCS-4	E425	Tracheostomy removed - counted as present in year, but not in subsequent years unless evidence of subsequent reinsertion
OPCS-4	E426	Tracheostomy present and assumed to remain until evidence of removal
OPCS-4	E427	Tracheostomy removed - counted as present in year, but not in subsequent years unless evidence of subsequent reinsertion
ICD-10	Z431	Gastrostomy present and assumed to remain until evidence of removal
ICD-10	Z931	Gastrostomy present and assumed to remain until evidence of removal
OPCS-4	G341	Gastrostomy present and assumed to remain until evidence of removal
OPCS-4	G342	Temporary gastrostomy - counted as present in year, but not in subsequent years unless evidence of subsequent permanent gastrostomy
OPCS-4	G343	Gastrostomy present and assumed to remain until evidence of removal
OPCS-4	G344	Gastrostomy removed - counted as present in year, but not in subsequent years unless evidence of subsequent reinsertion
OPCS-4	G345	Gastrostomy present and assumed to remain until evidence of removal
OPCS-4	G445	Gastrostomy present and assumed to remain until evidence of removal
OPCS-4	G447	Gastrostomy removed - counted as present in year, but not in subsequent years unless evidence of subsequent reinsertion

ICD-10 and OPCS-4 codes considered indicative of presence of gastrostomies or tracheostomies in a year and/or following years. ICD-10: International Classification of Diseases, 10th Edition; OPCS-4: OPCS Classification of Interventions and Procedures Version 4.

combinations of intersections and bar graphs above the matrix show the size of each intersection. To reduce the number of comparison groups for simplicity in the UpSet graph matrix, analyses were limited to indications of high complexity: intersections between membership of approximately the top 10% of each measure in the final year (2018/19) were compared to

see whether being in the top 10% on one measure was indicative of being in the top 10% for another. In addition, it was intended to use only one measure for each of the four second level aspects of complexity for which data were available: diagnoses, multiple service providers, high resource use and technology dependence (middle ring, Figure 2). Where an aspect of complexity had multiple measures (e.g., technology dependence, high resource use) UpSet graphs were used to analyse overlap between individual measures.

Results

Numbers and characteristics of young people aged 14–19 years with life-limiting conditions

A total of 121626 young people with life-limiting conditions diagnosed while aged 16 years or younger were identified in the data. From financial year 2012/13 to 2018/19, the number of young people aged 14-19 years with a life-limiting condition diagnosed at age 16 years or younger increased from 20363 to 34307 (Figure 3). Proportions in each year of age remained similar over time.

There were increases over the study period in the number of young people aged 14-19 years with each of the categories of life-limiting conditions (Figure 4). Congenital conditions remained the largest group throughout, increasing from 7201 in 2012/13 to 13230 in 2018/19. The proportion with congenital (2012/13: 35.4%; 2018/19: 38.6%), haematology (2012/13: 13.6%; 2018/19: 15.5%) and genitourinary conditions (2012/13: 9.5%; 2018/19: 12.0%) increased and the proportion with oncology conditions - for which a five-year limit from first

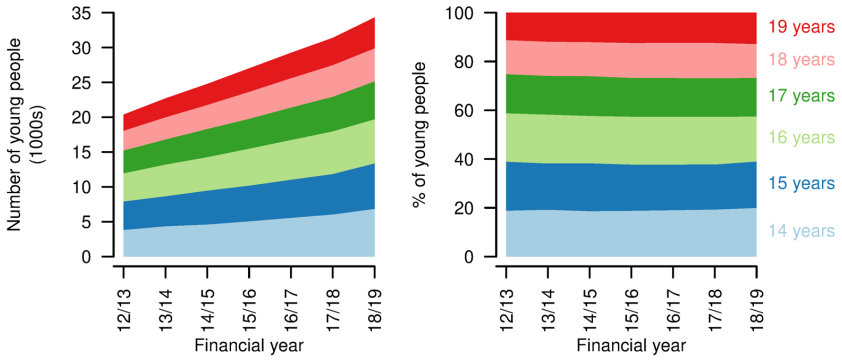

Figure 3. Numbers and ages of young people aged 14–19 years with life limiting conditions. Numbers (left) and proportions (right) of young people aged 14–19 years with a life-limiting condition, by age, by year.

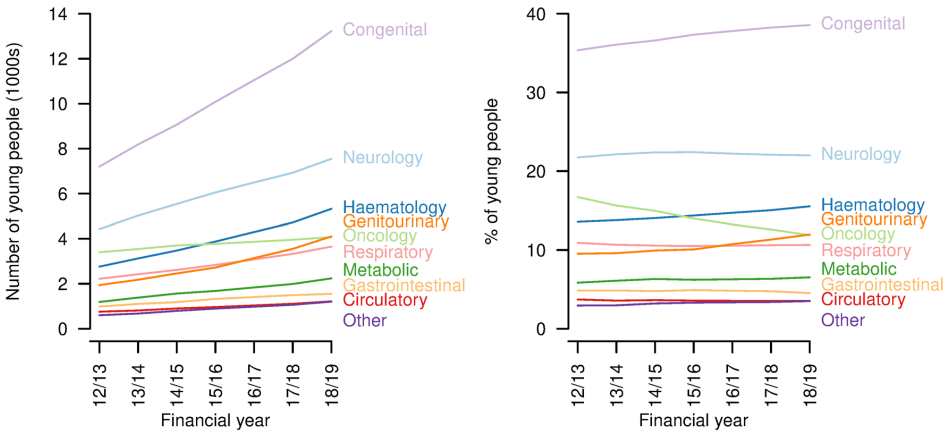

Figure 4. Categories of conditions of young people aged 14–19 years with life limiting conditions. Numbers (left) and proportions (right) of young people aged 14–19 years with a life-limiting condition with each category of condition, by year.

diagnosis was imposed, except for central nervous system tumours - decreased (2012/13: 16.7%; 2018/19: 11.9%) despite an increase in absolute numbers (2012/13: 3401; 2018/19: 4077). The proportions with other categories of condition remained largely constant.

The balance between recorded sexes remained similar over the study period, with more male than female patients (2012/13: 54.6% versus 45.4%; 2018/19: 54.0% versus 46.0%, Figure 5).

The number of young people in each ethnic group increased over the study period, but the proportion in the White ethnic group decreased (2012/13: 79.2%; 2018/19: 73.6%) as did the proportion in the Chinese ethnic group (2012/13: 0.31%; 2018/19: 0.22%, Figure 5). All other ethnic groups increased as a proportion, with the largest increases in the Mixed (2012/13: 1.6%; 2018/19: 2.4%) and Pakistani ethnic groups (2012/13: 4.8%; 2018/19: 6.4%).

There were increases in the number of young people aged 14-19 years with life-limiting conditions in each of the Government Office Regions (Figure 5). The largest proportional increase was in the West Midlands, where numbers grew by 98% over the study period (2012/13: 2319; 2018/19: 3785) and the smallest in the South West, where numbers grew by 51% (2012/13: 1957; 2018/19: 2959)

There were small variations in the proportion of young people in each deprivation category (Figure 5), with small movements towards less deprived categories, e.g., increases in those in group one (2012/13: 19.5%; 2018/19: 21.1%) and decreases in those in group five (2012/13: 20.8%; 2018/19: 19.6%). Overall, there was a very even distribution between deprivation categories.

Medical complexity

Chronic conditions. The number of distinct types of chronic condition (including life-limiting conditions) increased over the study period, with the largest proportional increase in the number of young people having eight or more chronic condition categories recorded, up from 7.6% in 2012/13 to 14.0% in 2018/19 (Figure 6). There was a decrease in those with only one chronic condition category recorded, from 18.2% in 2012/13 to 13.5% in 2018/19.

Healthcare use - multiple service providers. An increased proportion of young people with life-limiting conditions were treated by consultants across six or more main consultant specialties (2012/13: 7.9%; 2018/19: 11.0%, Figure 7). There was a fall in the proportion treated by consultants with four or fewer main consultant specialties and a small increase in those treated by consultants with five consultant specialties (2012/13: 7.4%; 2018/19: 7.9%).

Healthcare use - high resource use. There was a proportional (and absolute) increase in A&E visits per person per year, with a small drop in those having no A&E visits in a year (2012/13: 63.2%; 2018/19: 61.4%, Figure 8). Total A&E visits increased from 15241 in 2012/13 to 28019 in 2018/19.

Inpatient admissions per person per year decreased over the study period, with increases in those having no admissions in a year (2012/13: 52.8%; 2018/19: 60.3%, Figure 8). Proportions with more admissions reduced correspondingly. There was also a decrease in emergency admissions per person, although to a lesser extent, with an increase in those with no emergency admissions (2012/13: 76.6%; 2018/19: 79.9%, Figure 8). The proportion of young people with no inpatient bed days in a year increased over the study period (2012/13: 51.6%; 2018/19: 59.8%). The group with 29 or more inpatient bed days decreased proportionally the most (2012/13: 6.5%; 2018/19: 4.0%). Total bed days increased from 142557 in 2012/13 to 157298 in 2018/19.

Length of stay (for those spending at least one night in hospital - i.e., excluding day cases) also decreased slightly, with more young people having single night stays (2012/13: 20.8%; 2018/19 35.2%, Figure 8). There was, however, also an increase in the longest stays, of 29 days or more, up to 2017/18, at least (2012/13: 2.6%; 2017/18: 3.1%). Day cases increased from 62.3% to 65.0% of admissions over the same period.

Functional limitations. Numbers of young people with gastrostomies or tracheostomies increased over the study period (gastrostomies: 2012/23: 1801, 2018/19: 3143; tracheostomies: 2012/23: 208, 2018/19: 357; Figure 9). However, the proportions changed little for gastrostomies (2012/13: 8.8%; 2018/19: 9.2%, but with variation in both directions over the period) and did not vary between the start and end of the study period for tracheostomies (1.0%).

Overlaps between measures of complexity. Analysis of intersections between the five measures of high resource use showed little overlap between being in the top 10% for A&E visits and the other indicators (Figure 10) so two indicators were retained - being in the top 10% for A&E visits and being in the top 10% for bed days (this being the most interconnected of the remaining measures and combining aspects of numbers of admissions and length of stay). Presence of a gastrostomy was retained as the measure of technology dependence, due to the low number (approximately 1%) with tracheostomies and the high overlap of those with tracheostomies also having gastrostomies (70%, Figure 10). As a result, membership of the top 10% of five measures in 2018/19 was compared: diagnoses (number of chronic conditions); multiple service providers (number of distinct consultant main specialties); technology dependence (presence of a gastrostomy); resource use (A&E visits and bed days, Figure 10).

The number of young people present in the top 10% of any of the five measures in 2018/19 was 11488 (33% of all young people present in 2018/19). There was limited intersection between the five groups. The five largest categories were for each of the groups alone and totalled 5945 - i.e., 52% of those in the top 10% for any of the five measures were only in the top

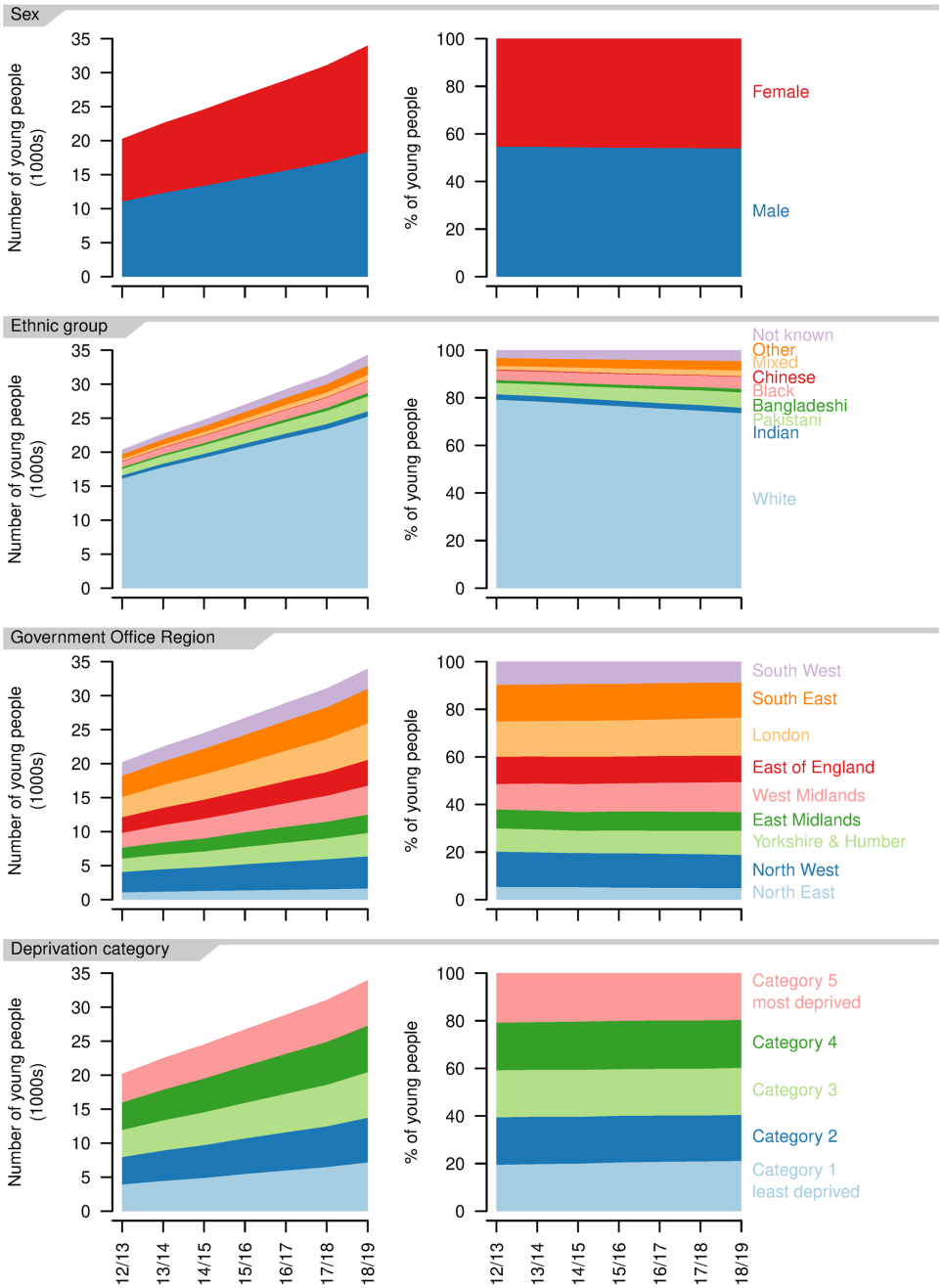

Figure 5. Demographics of young people aged 14–19 years with a life-limiting condition. Numbers (left) and proportions (right) for each recorded sex, ethnic group, Government Office Region of residence and deprivation category, by year.

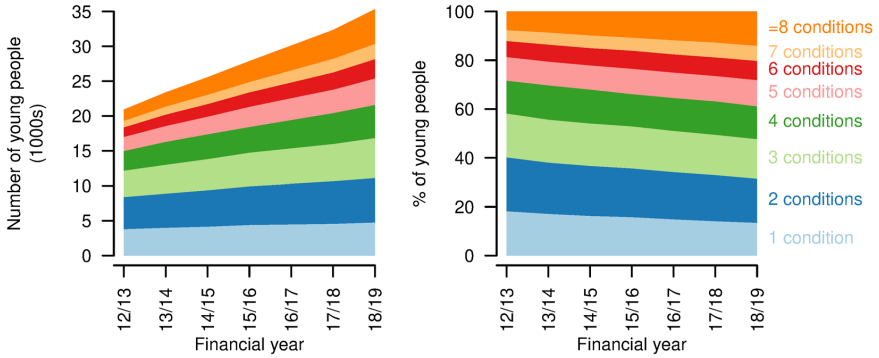

Figure 6. Numbers of chronic conditions for young people aged 14–19 years with a life-limiting condition. Numbers (left) and proportions (right) of young people aged 14–19 years with a life-limiting condition having different numbers of chronic condition categories recorded, by year.

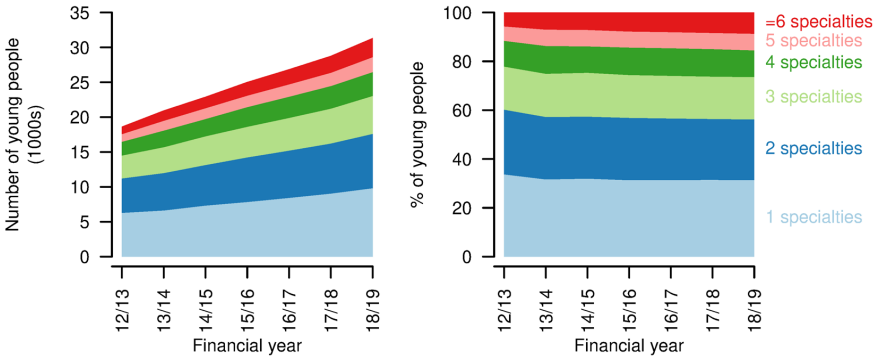

Figure 7. Numbers of main consultant specialties for young people aged 14–19 years with a life-limiting condition. Numbers (left) and proportions (right) of young people aged 14–19 years with a life-limiting condition receiving treatment from consultants under different numbers of consultant main specialties in each year.

10% for one of the measures. Only 1.2% were in the top 10% for all five measures. However, overlap was seen between technology dependence and number of diagnoses - 5% of those in the top 10% on any measure were in the top 10% for both technology dependence and number of diagnoses - and to a lesser extent between bed days and multiple service providers and between diagnoses and multiple service providers. Overall, high numbers of diagnoses (being in the top 10%) was more indicative of being in the top 10% on at least one other measure than the other four measures - 75% of those in the top 10% for number of diagnoses were also in the top 10% for one of the other measures. This compared to 50% for A&E visits, 40% for technology dependence and 35% for bed days.

Discussion

This study shows increasing numbers of young people with life-limiting conditions reaching the ages at which they transition to adult healthcare. There is also evidence of increased complexity with regard to numbers of recorded chronic conditions and consultants of different specialties seen, but limited evidence for increased instability or hospital healthcare use. It was found that 33% of young people with life-limiting conditions reaching the ages at which they transition to adult healthcare were in the top 10% on at least one of the five measures of complexity, indicating that medical complexity is common in this population.

The increase in numbers of young people with life-limiting conditions at transition ages and with their conditions first diagnosed in childhood is large - 68% larger in 2018/19 than 2012/13. It shows increasing proportions with congenital, haematology and genitourinary diagnoses and a falling proportion with oncology diagnoses who are within five years of first diagnosis (for non-central nervous system tumours)

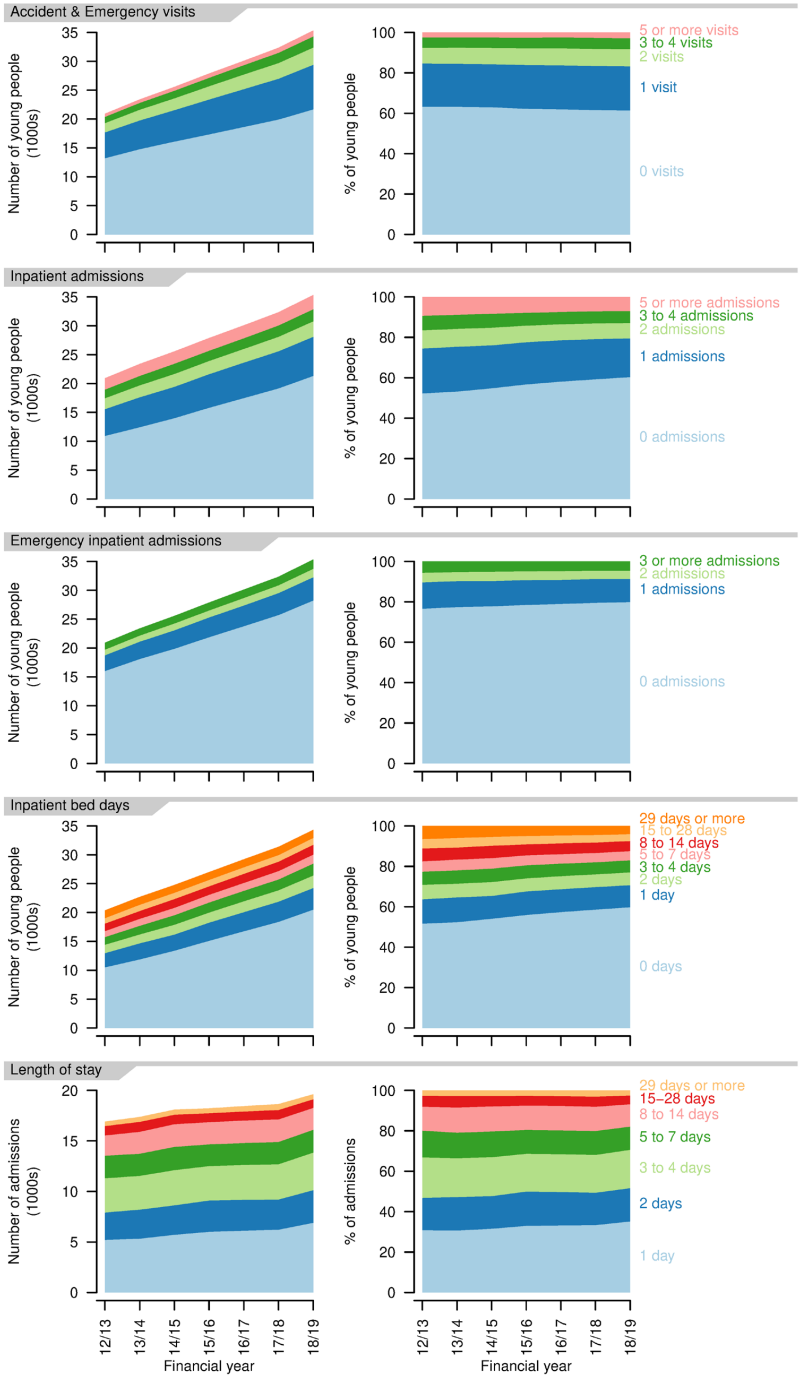

Figure 8. Indicators of high resource use for young people aged 14–19 years with a life-limiting condition. First four rows: numbers (left) and proportions (right) of young people having different numbers of Accident & Emergency visits, inpatient admissions, emergency inpatient admissions, bed days in each year. Final row: numbers (left) and proportions (right) of inpatient admissions of differing lengths in each year.

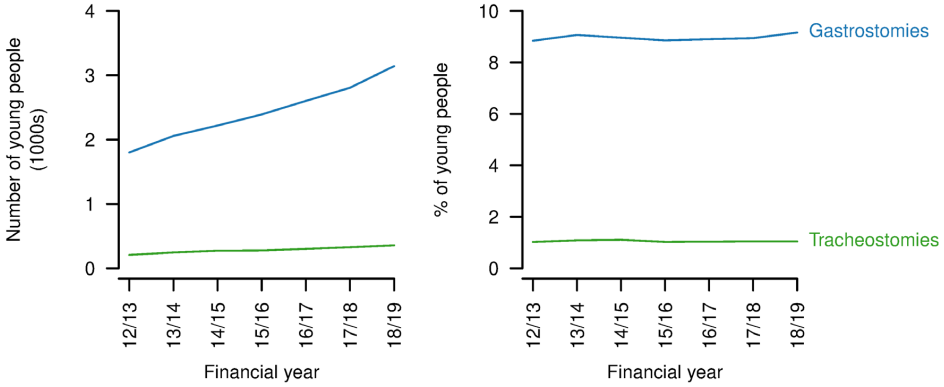

Figure 9. Technology dependence for young people aged 14–19 years with a life-limiting condition. Numbers (left) and proportions (right) of young people aged 14–9 years with a life-limiting condition also having a gastrostomy or tracheostomy present in each year.

although this group still increased in absolute terms. There has been an increase in those from non-White ethnic groups, particularly the Mixed and Pakistani ethnic groups. By region, the biggest proportional increases have occurred in the West Midlands.

This study is, to the best of the authors' knowledge, the first attempt to describe medical complexity in young people with life-limiting conditions on a national scale using routinely collected data. It found that there was an increase in the numbers of young people with more different categories of chronic condition recorded, particularly among those with eight or more categories recorded. Similarly, there was an increase in the proportion treated by consultants with six or more distinct main consultant specialties in a year. There was however also an increase in the proportions with no inpatient and no emergency inpatient admissions, although a small increase in those with one or more A&E visits in a year. For length of stay, there were both increases in those having single night inpatient stays and those having the longest stays (29 nights or more). There was an increase in those having no inpatient bed days in the year and a marked decrease in those having 29 or more bed days. The proportion with gastrostomies increased from 8.8% to 9.2%, but there was no notable change in the proportion with tracheostomies.

The lack of overlap between young people in the top 10% of most of the measures of complexity suggests that complexity is, as previously suggested[20,23], a multi-faceted phenomenon and that multiple measures are required for assessment. Numbers of distinct chronic diagnoses were the strongest indicator of complexity in other categories, with 75% of those in the top 10% for number of diagnoses also in the top 10% for at least one of the other measures.

Comparisons with previous studies

In common with a previous study covering a similar time period[1], this study found an increasing number of young people with life-limiting conditions, but the numbers of young people aged 14–19 years with a life-limiting condition diagnosed in childhood showed a greater proportional increase in this study compared to the previous study. This may be due to the previous study not separating those with conditions first diagnosed in childhood from those with conditions first diagnosed in adulthood. If increases in survival, rather than incidence, are the main driver for increased numbers of young people with life-limiting conditions then it would be expected that there would be a greater increase in those with life-limiting conditions diagnosed in childhood (driven by increased survival) than those diagnosed as adults (driven mostly by incidence).

In contrast to the previous study looking at a 0–19 year old population with life-limiting conditions[1], there was a close to even distribution across the deprivation categories in this study, rather than larger numbers in the most deprived categories. This may be due to differences in conditions (with differing life expectancies) between deprivation categories or due to differences in survival times for a given condition dependent on deprivation category. There is evidence of differential survival or progression for some conditions depending on deprivation status[32,33] although not all studies show this[34].

While there are no other studies looking nationally at medical complexity among young people with life-limiting conditions at transition ages in England, there is a study looking at complexity among children and young people with disabilities at a single centre[23]. This used a measure of complexity combining numbers of conditions, family reported issues and technology dependence. It found that the children most commonly had one to three issues, with a decrease in numbers with more issues but a significant group with 10 or more issues. This is similar to some of the findings in the present study, for example that young people of transition ages are most likely (18.0%) to have two distinct chronic conditions reported, a drop off in numbers with more conditions but a significant group (14.0%) with

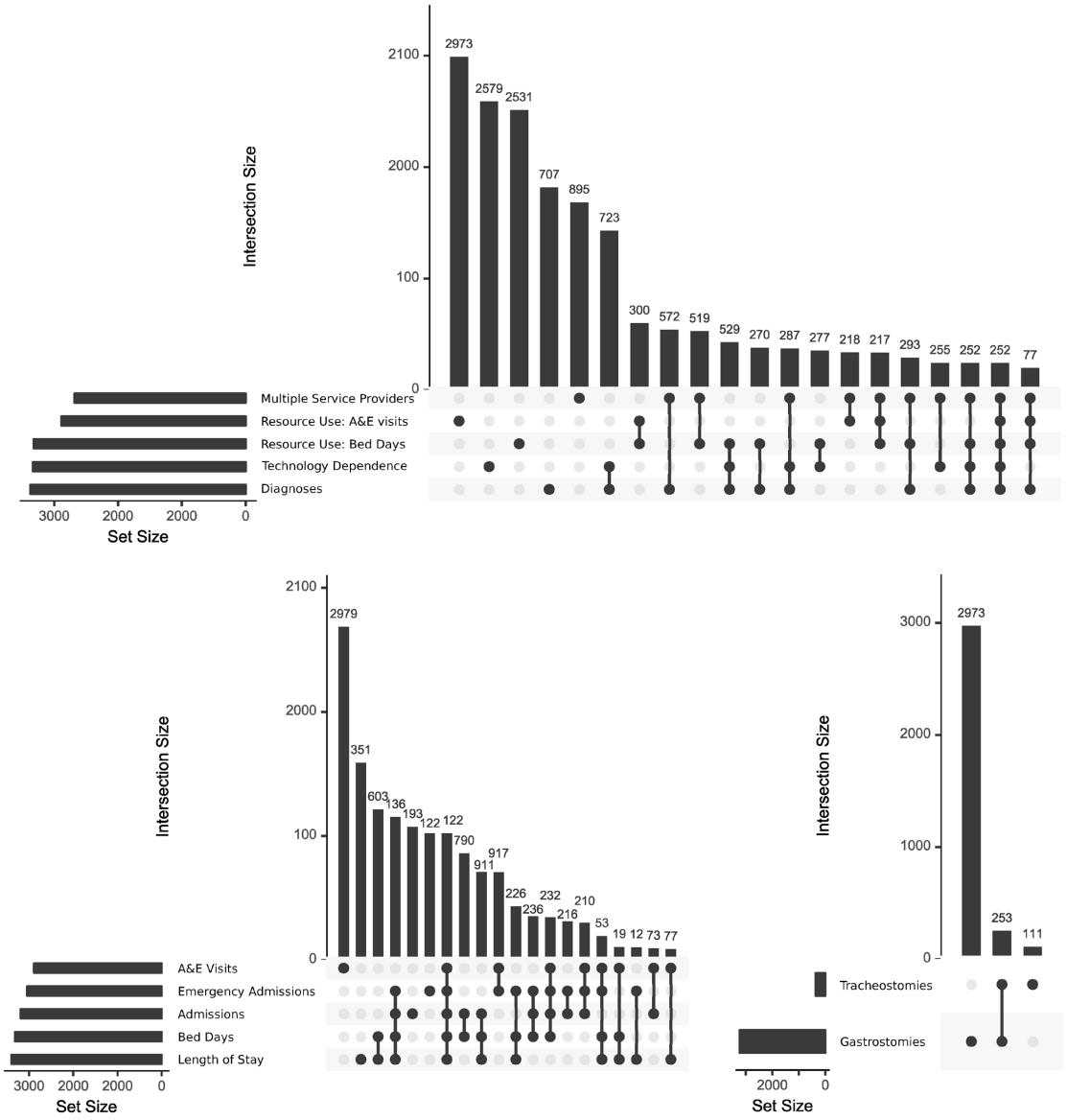

Figure 10. UpSet graphs showing relations between measures of complexity. Intersections between (top) those in approximately the top 10% for each of five indicators of complexity; (bottom left) those in approximately the top 10% in each of the five indicators of high resource use; (bottom right) those with technology dependence. For simplicity, only the largest 20 intersections are shown.

eight or more conditions. Also, while numbers of young people decreased with increasing numbers of consultant main specialities recorded in a year, 11.0% had more than six. These young people with greater medical complexity may be expected to have more healthcare use[23].

There are also studies from North America that quantify numbers of children with medical complexity[21,35–37]. Unlike the present study, these studies have not looked at trends in complexity over time, but have attempted to quantify sizes of populations with medical complexity, under varying definitions, finding

between 0.4% and 6% of study populations to be complex. The present study did not define a cut-off for having or not having medical complexity, focusing instead on whether there were changes in the level of complexity over time.

There was a lack of evidence for increases in inpatient healthcare use per person in the present study. This corresponds with previous findings on falls in length of stay and bed days per person in a related population with neurological conditions[38] and increased clinical stability in young people with life-limiting conditions in Scotland[4]. Increased survival times for life-limiting conditions may be accompanied by increased time in a relatively stable state - while young people with greater medical complexity may increasingly be surviving to transition ages, those who were already surviving to these ages may be more stable than in the past. Better management in the community, in primary care and allied services, may reduce the need for inpatient admissions in this population[39]. Inpatient admissions and A&E visits are still much higher among young people with life-limiting conditions than in the general population[24,25,40].

This study found increases in the numbers of young people with gastrostomies present, in line with previous analyses of HES data in England[41] and similar data in a related population in Australia[42]. In line with the Australian study, there was little evidence for changes in the proportions of young people with life-limiting conditions at transition ages with gastrostomies. The increase in absolute numbers does however represent an increasing number of young people with high care needs. Estimated numbers with tracheostomies from the present study are comparable to that in a recent report on long term ventilation[43], but that report looked at ages 0-24 years and was not restricted to those with life-limiting conditions. It did, however, only collect data from hospitals considered long term ventilation centres, in contrast to the present study using data from all NHS hospitals in England. The present study may also include some individuals not on long term ventilation.

Other studies have looked at overlap between indicators of complexity[23,24]. Although measures differed, they also found that multiple chronic conditions were associated with greater levels of technology dependence, including gastrostomies[24] and that it is not unusual for a young person with complex healthcare needs to present with only one or two aspects of complexity[23]. Multiple measures are needed to identify young people with complex healthcare needs.

Implications for policy

This study shows that the population with life-limiting conditions likely to need transition to adult care is increasing rapidly. This is particularly true for the non-White ethnic groups, underlying the importance of transition programmes that serve all sectors of the community. There were also differences in the rate of increase by Government Office Region, suggesting some areas may have greater increases than others in resource use for young people of these ages.

Increasing numbers of chronic conditions present and numbers of distinct consultant main specialties required for care has implications for the complexity of transition. A number of transitions between care teams treating different aspects of a young person's condition and associated co-morbidities are likely to take place. This increases the need for coordination between care teams, not only paediatric and adult but also across different specialties, which may improve care and reduce unnecessary healthcare use[24,25,44–47].

While there was a lack of evidence for increases in some aspects of hospital healthcare use per person, the rapidly increasing size of the population means that absolute numbers of admissions, emergency admissions, A&E visits and bed days are increasing greatly. This study also shows that one third of children and young people with life-limiting conditions are in the top 10% on at least one measure of complexity. Service planners will need to be aware of this.

There is evidence that emergency healthcare use increases when young people with life-limiting conditions in England transition to adult care[48] and wider evidence for an increase in A&E visits[49]. As the population undergoing transition increases in size, this will increase pressures on healthcare systems and mean that a larger group is impacted by any negative experiences of emergency care. It is increasingly important for experiences of young people and for efficient healthcare resource to optimise transition processes.

Implications for future research

This research leaves some unanswered questions. There is a disconnect between the apparent increasing complexity of the population reaching transition ages, at least in terms of diagnoses and numbers of consultants from different specialities involved in care and the lack of evidence for similar increases in hospital care use. Further research looking at individual conditions or closely related groups of conditions and at the last few years of life would be needed to assess whether increased survival is accompanied by longer periods of stability and whether this varies across conditions. In addition, there may be a lack of specificity in the coding framework for life-limiting conditions, due to a lack of specificity in ICD-10 diagnostic codes or due to changes in the diagnoses that should be considered life-limiting. Studies including primary care may give insights into whether care is moving more into the community for this population, with perhaps more or more frequent primary care contact replacing hospital admissions. Analysis of community prescribing would also provide information on whether patterns of prescribing are indicative of an increasingly stable population and potentially give insights on other aspects of complexity, e.g. polypharmacy[20].

There is also a need for additional qualitative research in this population to understand medical complexity as experienced by young people, families, and clinicians and for research to develop better methods of measuring these from the available data.

Smaller studies reviewing medical records or using mixed methods may provide greater insights, particularly on aspects of medical complexity not investigated in this study.

Strengths and limitations

This study has a number of strengths. It draws upon established frameworks for defining medical complexity and identifying young people with life-limiting conditions. It uses national, whole-population data and so is representative with respect to the population of England. The methods are reproducible, enabling further updates to monitor changes into the future or application of alternative conceptualisations of medical complexity.

There are also limitations. Notably, several aspects of medical complexity previously identified[20] cannot be assessed at all with the data used. In particular, the data are silent on family experiences and on measures of condition severity. As suggested above, these might be addressed through smaller and mixed method studies. There are also inevitable limitations to analysing data on a large scale, in the level of detail possible in defining life-limiting conditions, categories of life-limiting conditions and categories of distinct chronic conditions. While these were based on previously developed frameworks, other categorisations would be possible and may result in different findings.

Conclusions

The group of young people with life-limiting conditions reaching ages at which transition to adult healthcare should take place is increasing rapidly, more quickly than for the population of children and young people with life-limiting conditions as a whole. This group is also increasing in medical complexity as far as numbers of conditions and numbers of consultant main specialties required for treatment and one third of included young people were in the top 10% for at least one measure of complexity. The increasing size of the group also means that use of hospital care, including emergency care, is increasing. There is limited overlap between measures of complexity, so multiple measures are required.

Healthcare providers will need to allocate resources to deal with increasing healthcare demands and greater complexity in conditions present and numbers of different care teams involved. Transition to adult healthcare must be managed well to limit impacts on healthcare resource use and improve experiences for young people and their families.

Data availability

Underlying data

The data used in this study are personal healthcare data used under agreement from NHS Digital. The individual data cannot be shared under the data sharing agreement. Other researchers are free to apply for similar data from NHS Digital through the Data Access Request Service. The data requested from NHS Digital were all records up to age 23 years for all children and young people who were aged 12–23 years at any point between 1 April 2007 – 31 March 2019 from the following datasets:

- Hospital Episode Statistics 'Admitted Patient Care' dataset (records from 1 April 2006 – 31 March 2019)
- Hospital Episode Statistics 'Outpatient' dataset (records from 1 April 2006 – 31 March 2019)
- Hospital Episode Statistics 'Accident & Emergency' Department dataset (records from 1 April 2007 – 31 March 2019

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The supplementary materials are provided in Appendix 2, beginning on page 125, including:

Please see Section 9.2 for discussion of other relevant issues identified since publication of this paper.

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Pediatric RESEARCH

SYSTEMATIC REVIEW OPEN

Transition of children with life-limiting conditions to adult care and healthcare use: a systematic review

Stuart W. Jarvis[1], Daniel Roberts[2], Kate Flemming[3], Gerry Richardson[4] and Lorna K. Fraser[1]

BACKGROUND: Improved survival has led to increasing numbers of children with life-limiting conditions transitioning to adult healthcare services. There are concerns that transition may lead to a reduction in care quality and increases in emergency care. This review explores evidence for differences in health or social care use post- versus pre-transition to adult services.
METHODS: MEDLINE, EMBASE, CINAHL, PsychINFO and Social Science Citation Index were searched. Studies published in English since 1990 including individuals with any life-limiting condition post- and pre-transition and reporting a health or social care use outcome were included. Data were extracted and quality assessed by one reviewer with 30% checked by an independent reviewer.
RESULTS: Nineteen papers (18 studies) met the inclusion criteria. There was evidence for both increases and decreases (post- versus pre-transition) in outpatient attendance, inpatient admissions, inpatient bed days and health service costs; for increases in Emergency Department visits and for decreases in individuals receiving physiotherapy.
CONCLUSIONS: Evidence for changes in healthcare use post- versus pre-transition is mixed and conflicting, although there is evidence for an increase in Emergency Department visits and a reduction in access to physiotherapy. More high-quality research is needed to better link changes in care to the transition.

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IMPACT:

- Evidence for changes in healthcare use associated with transition to adult services is conflicting.
- Emergency Department visits increase and access to physiotherapy decreases at transition.
- There are marked differences between care patterns in the United States and Canada.

INTRODUCTION

Life-limiting conditions (LLCs) include conditions that limit life—i.e. cause premature death, such as Duchenne muscular dystrophy, Batten's disease and conditions that threaten life—i.e. may cause early death but may be cured, such as cancer or liver failure. There are increasing numbers of children and young people with LLCs.[1,2] Although individual conditions are rare, there are many more children and young people with LLCs in the United Kingdom (approx. 85,000 in 2017/18[3]) than with diabetes mellitus (approx. 36,000 in 2018[4]) and at least 500,000 children living with similar conditions in the United States.[5]

Children with LLCs often receive specialist paediatric care before transitioning to adult services, typically from age 16 to 19 years in the United Kingdom[6] and planned to be around age 18 years in the United States.[7] There are many differences in delivery of paediatric and adult care, including relationship continuity and condition expertise.[6,8] In childhood, allied health services, such as physiotherapy, are provided on an ongoing basis in the UK. There may be direct access to a specialist hospital ward when needed without having to first go through primary care or an Emergency Department. Care is often coordinated by the paediatric specialist with parents directly involved in decisions.[9] Adults may have care coordinated by a primary care practitioner, with little experience of their condition and with whom they may have had little childhood contact. Allied health services are booked in blocks, with possible gaps in provision (there may be no equivalent adult service).[10] Hospital access may require primary care or Emergency Department referral.[11] Where the young people have capacity, they are expected to take more responsibility for care and care decisions, reducing parental involvement.[9]

The transition can be poorly defined and care may also continue in paediatric settings.[12] Primary care transition training can be lacking, despite efforts at improvement.[8] Transition can appear abrupt[6,13] and support varies between conditions, but staff continuity, specialist adolescent clinics, good communication and planning are vital.[6] Guidelines in the United Kingdom and United States highlight the challenges and need for planning.[9,14] The United Kingdom Chief Medical Officer's report[8] into child health called for more research on transition for children with long-term conditions.

Systematic reviews have mainly focussed on transition experiences, interventions and biological indicators of disease progression, not healthcare use.[15–19] Two reviews looked at experiences and found that many young people felt they lacked knowledge about their conditions, felt unprepared and feared that adult providers had similar limitations.[15,17] One assessed loss to follow-

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up and lapse of care, reporting losses of between 7 and 61% depending on country and definition used.[15] Other reviews considered healthcare use, but from the perspective of whether there was continuity of care, not quantifying differences in (for example) contacts post- versus pre-transition.[16,18] These found poor continuity and no standardised transition with, instead, condition-specific programmes. Where biological indicators were assessed, they were commonly compared between intervention and control groups rather than post- versus pre-transition.[18,19]

In short, appraisal of the evidence for changes in healthcare post- versus pre-transition is lacking. Changes are likely to be important to young people and their families. Any increases in (for example) emergency hospital care may have negative implications for them through emotional trauma, disruption and (also, potentially, for health service providers) financial costs.[20–25]

This systematic review aimed to assess evidence for a change in health or social care use for young people with LLC post- compared to pre-transition. This information is needed to identify conditions and areas of care where use varies across the transition, useful for targeting future interventions and research.

METHODS

The protocol was registered on PROSPERO[26] (ref. CRD42019156282.[27]). Reporting follows the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA)[28] and Synthesis Without Meta-Analysis[29] guidelines.

Eligibility criteria

Observational studies, randomised controlled trials and studies using quasi-experimental methods (e.g. interrupted time series, regression discontinuity) published in English from 1990 onwards were included if meeting the following criteria (presented in the Population, Exposure, Outcome format). Studies published before 1990 were excluded as widespread survival to adulthood in the LLC population is a relatively recent phenomenon, making older studies less relevant. Systematic reviews were not included, but for any reviews otherwise meeting inclusion criteria, the studies in the review were considered for inclusion.

Population. Children and young people with a LLC, including those treated in both paediatric and adult services (or, if assignment to post- and pre-transition groups was not explicit, including a range of ages spanning at least 15–19 years of age), in Organisation for Economic Co-operation and Development countries. The country limitation avoided comparisons with countries with potentially very different epidemiology and treatment of conditions—e.g. higher prevalence and poorer outcomes for HIV in many developing countries.[30] Where a study included conditions that may or may not be LLC, depending on severity (e.g. cerebral palsy) only subgroups judged to have a LLC (if provided) were included.

Exposure. The transition from paediatric to adult healthcare services (i.e. in outpatient, inpatient and primary care).

Outcomes. Any measures of health or social care use, excluding those that were purely prescribing (e.g. intravenous antibiotic courses were of interest, oral antibiotic courses were not). Outcomes identified a priori were hospital admissions, bed days, Emergency Department visits, primary care visits and overall costs (direct costs to providers and direct or indirect costs to children and young people and their families).

Assignment to paediatric or adult groups. Study assignments to post- and pre-transition groups were used. It was planned, for any studies that neither assigned individuals to groups nor defined age of transition, to assign the group up to and closest to 16 years as pre-transition and the youngest group aged ≥19 as post-transition, based on common transition ages in the countries studied.[6–8] However, these rules were not used as all included studies did their own assignment.

Information sources

MEDLINE, EMBASE, CINAHL, PsychINFO and Social Science Citation Index were searched from 1 January 1990 to 27 April 2020 (date of last search). Forward and reverse citation searching was used for the included studies.

Search strategy

The search strategy (supplementary material) was developed using the following concepts:

- LLC (using previously developed search strategies[31])
  AND
- Children/young people (extended from published search strategies[14,15,19,32–35])
  AND
- Transition (extended from published search strategies[14,15,19,32,34])

Study records

Records were de-duplicated using Endnote[36] and uploaded to Covidence[37] for screening.

Selection process

One reviewer (S.W.J.) screened titles and abstracts against the eligibility criteria. A second reviewer (D.R.) independently screened 20%. Where disagreements occurred, records were retained for full-text screening.

Final selection used full-text records, with two reviewers (S.W.J. and D.R.) assessing all records. A third reviewer (L.K.F.) resolved disagreements.

Data extraction and quality assessment process

One reviewer (S.W.J.) extracted data and assessed quality, with 30% checked by a fourth reviewer (D.G.-S., see "Acknowledgements"). Disagreements were resolved by discussion. Extracted data items are listed in the extraction form (Supplementary Material). Quality was assessed using a modified Newcastle–Ottawa scale[38] (Supplementary Material) with one inapplicable question omitted (demonstration that the outcome of interest was not present at the beginning of the study).

Summary measures

Outcome data were transformed to standardised measures where possible[39]: mean difference or incidence rate ratio where numbers of outcomes were reported and odds ratios where percentage risk or relative risk was reported. Some reported measures (medians, median differences) were not transformable.

Data synthesis

A meta-analysis was planned,[27] but studies were insufficiently comparable to undertake this (see "Results"). Alternative approaches were considered: summarising effect estimates[40] was rejected for similar reasons to conducting a meta-analysis (study designs and measures were too heterogeneous). Instead, *p* value combination[40,41] and vote counting[40] were used. Data were synthesised by outcome as differences by outcome were of interest (i.e. not only whether care use changed but for which outcomes).

p Value combination summarises the strength of evidence for an effect by combining *p* values reported in studies with a common effect direction. Fisher's *p* value[41] was used as a summary measure, indicating whether at least one study showed evidence of an effect. This was visualised using albatross plots,[42] which plot *p* value and effect direction against sample size. Visual

guidelines show the expected plotting position of studies of differing sample sizes with the same effect size—if the true effect size of an intervention was a standardised mean difference of 0.1, then studies of different sizes would cluster around this guideline. Missing *p* values were estimated from 95% confidence intervals (CIs)[43] or Fisher's exact test.[44]

As not all studies provided *p* values or data from which these could be estimated, vote counting (counting studies showing effects in each direction, irrespective of statistical significance[45]) was also conducted. This was visualised using harvest plots,[46] bar plots showing the number of studies (number of individual bars) reporting effects in each direction (irrespective of significance) and no effect and their quality scores (height of bar).

Assessment of reporting bias and the strength of the body of evidence

Low numbers of studies with directly comparable effect measures (<10 for all outcomes[47]) prevented the use of funnel plots and associated statistical tests for reporting bias.

Overall strength of evidence was planned[27] to be assessed using the GRADE framework.[48] As no overall effect sizes were estimated, this was not done.

RESULTS

Nineteen papers met inclusion criteria (Table 1) reporting on 18 observational studies—1 study was reported in 2 papers.[49,50] One systematic review[51] was also found to be relevant, but its relevant included studies had already been identified in the search and screening process. Figure 1 provides the PRISMA[28] diagram.

Study characteristics

Settings. Studies took place in six countries: Australia, Canada, France, Germany, United Kingdom, and United States (Table 1), with 12 from North America. Settings ranged from single clinics and hospitals to regional or national analyses. Data sources were mostly routinely collected medical records but included one multiple wave longitudinal cohort study[52] and one survey.[53]

Conditions studied. Six specific conditions were studied: renal conditions (end-stage kidney disease and kidney transplant recipients), HIV, sickle cell disease, cystic fibrosis, cerebral palsy, and spina bifida. Two studies[54,55] looked at multiple conditions.

Study designs. Ten studies had longitudinal cohort designs (the same individuals compared post- and pre-transition) and eight were cross-sectional (different individuals compared post- and pre-transition). One of the latter[56] used matching and one was a survey.[53]

Study quality. The observational studies varied in quality, scoring from 2 to 7 of a maximum of 8 on the customised Newcastle–Ottawa scale (Fig. 2). The scale assessed quality of studies for answering the review question—a low score does not necessarily mean that the study was of low quality for its own research question.

Representativeness of study population. Five studies[53,57–60] used pre-transition groups that were likely not representative of the larger population with the condition (e.g. they used data from a single clinic). The populations included in these studies were likely to reflect the demographics (for example, ethnic group, deprivation level) of individuals geographically close to the clinic and—where care was provided under private insurance—in possession of appropriate health insurance, rather than the population in the country with the condition. Studies scoring 1 on this criterion used population data (e.g. routine medical records at the nation or state level) or described how participants were representative. All studies drew the post-transition group from the same population as the pre-transition group and so satisfied the second criterion of a representative (of the membership of the pre-transition group) post-transition group.

Ascertainment of transition. The majority of studies used age to allocate individuals to paediatric and adult groups. Nine[49,50,52–55,61–63] did not provide justification (e.g. that transition invariably happened at that age), so misclassification bias was likely. Seven studies identified transition using clinical records and allowed individuals to transition at different ages.

Controlling for differences between groups. Eight studies[55–57,59,60,64–66] controlled for age or, where relevant, other differences between groups. Only three[53,56,66] controlled for severity of condition.

Ascertainment of outcomes and adequacy of follow-up. Most studies used medical records to measure outcomes; the three that did not[52,53,67] relied on recollection by the young person or service provider. Follow-up was of sufficient length (at least 1 year both post- and pre-transition) in all but two studies,[53,55] in which minimum follow-up was not stated. Follow-up was inadequate (>10% loss without analysis of potential bias) in 8 studies.[52,53,55,56,58,60,61,66]

Outcomes

Reported outcomes were: outpatient attendances, inpatient admissions, Emergency Department visits, inpatient bed days, intravenous antibiotic courses, physiotherapy, HIV care, General Practice contact, and healthcare costs (Supplemental Table 1).

Data synthesis

A meta-analysis was not conducted as the studies were too heterogeneous in designs (cross-section versus cohort), study populations (North America versus Europe; widely different age ranges in the groups compared) and outcome measures (mean differences, median differences, incidence rate ratios) to provide enough comparable studies for any outcome.

Outpatient attendances. Eleven studies reported outpatient attendance, five showed a lower number post- compared to pre-transition and six showed a higher number (Fig. 3). Quality of studies varied, with Newcastle–Ottawa scores (NOSs) of 3–7. *p* values were derivable for ten studies. There was strong evidence for both a reduction in at least one study (Fisher's $p < 0.001$) and an increase (Fisher's $p < 0.001$). Canadian studies all showed an increase while studies from the United States all showed a decrease. Studies that did not justify assignment to post- and pre-transition groups showed larger increases in outpatient attendance than most studies that did justify assignment.

Inpatient admissions. Ten studies looked at inpatient admissions. Six showed a decrease post-transition; four showed an increase (Fig. 3). Studies with results in both directions were of moderate-to-high quality (NOS = 4–7). *p* values were provided or derivable for nine. There was strong evidence for both a reduction (Fisher's $p < 0.001$) and an increase (Fisher's $p < 0.001$). Canadian studies all showed a decrease; United States studies showed increases and decreases, but only strong evidence for an increase (Fisher's *p* values: increase <0.001; decrease 0.87). Most studies showing a decrease post- versus pre-transition did not justify assignment to the post- and pre-transition groups.

Emergency Department visits. Five studies looked at changes in Emergency Department visits. Three showed an increase, one a decrease[60] and one no change[54] (Fig. 3). Studies were of moderate quality (NOS = 3–5). *p* values were derivable for four studies. There was strong evidence for an increase in Emergency Department visits (Fisher's $p < 0.001$). Two of the three studies showing an increase did not justify assignment to the post- and pre-transition groups.

Table 1. Characteristics of the included studies.

Study (ID)	Condition	Country	Setting	Design	Focus	Sample size	Groups compared	Outcomes	Measures	Transformed measures	Conclusions
Young et al.[49,50] (01)	Cerebral palsy	Canada	6 treatment centres, Ontario	X-section	Age-related treatment patterns	1064	13–17 years (mean 15.3) versus 23–32 years (mean 26.4)	OP attendances ED visits IP admissions Bed days	Mean per person per year	IRR Mean difference	Decrease in OP attendances Decrease in IP admissions
Liljenquist et al.[52] (02)	Cerebral palsy	USA	National cohort study	Historical longitudinal cohort	Physio during transition	35,290	Cohort: 13–16 years versus 21–26 years	Receipt of physiotherapy	% having visit per year	OR (but different and unknown time base)	Decrease in physiotherapy after transition
Roquet et al.[53] (04)	Cerebral palsy	France	Brittany—survey	X-section (survey)	Healthcare use differences across transition	54	12–17 years versus 18–24 years	GP visits Receipt of physiotherapy	% having visit per year	OR	Decrease in rehabilitation service use
Duguépéroux et al.[65] (04)	Cystic fibrosis	France	Single clinic	Longitudinal cohort	Clinical changes during transition	68	One year before transition versus 1 year after (median transition age 21 years)	OP attendances IV antibiotic courses Receipt of physiotherapy	Mean per person per year % having visit per year	IRR Mean difference OR	No negative impact
Tuchman and Schwartz[56] (05)	Cystic fibrosis	USA	National registry	X-section (matched)	Health outcomes at transition	1322	Transitioned compared 1 year after transition to matched the non-transitioned group	IP admissions IV antibiotic courses	Mean per person per year	IRR Mean difference	No change
Collins et al.[58] (06)	Cystic fibrosis	Australia	Single hospital	Longitudinal cohort	Hospital attendance at transition	44	Two years before transition versus 2 years after	OP attendances Bed days Days on IV antibiotics	Mean difference	Mean difference	Increase in OP visits, IP admissions and home IV antibiotic days
Crowley et al.[59] (07)	Cystic fibrosis	USA	Single clinic	Longitudinal cohort	Association between social complexity and outcomes after transition	133	Two years before transition versus 2 years after	OP attendances Inpatient admissions	Mean per person per year	IRR Mean difference	Decrease in OP visits
Welsner[104] (08)	Cystic fibrosis	Germany	Single hospital	Historical longitudinal cohort	Clinical changes during transition	39	1 year before transitions compared to 1 year after	Outpatient attendances Inpatient admissions	Mean per person per year	IRR Mean difference	Increase in OP visits and IP admissions
Biersteker[57] (09)	HIV	USA	Single clinic	Longitudinal cohort	Outcomes of transition	25	1 year before transition compared to 1 year after	Outpatient attendances	Median per person per year	—	Decrease in OP attendance
Gray et al.[62] (10)	HIV	USA	National registry	X-section	Care outcomes for those with HIV	3111	13–17 year olds versus 26+ years	Receipt of HIV care	% having visit per year	OR	Decrease in care
Akchurin et al.[64] (11)	Renal	Canada	Single clinic	Historical longitudinal cohort	Medication adherence at transition	25	19–32 years versus to 9–17 years	OP attendances IP admissions ED visits	Mean per person per year	IRR Mean difference	Decrease in IP admissions Increase in ED visits

Table 1. continued

Study (ID)	Condition	Country	Setting	Design	Focus	Sample size	Groups compared	Outcomes	Measures	Transformed measures	Conclusions
Pape et al.[67] (12)	Renal	Germany	Single clinic	Longitudinal cohort	Comparing transition routes	59	1 year before transition to 1 year after	OP attendances	Mean per person per year	IRR Mean difference	No significant change
Samuel et al.[66] (13)	Renal	Canada	National registry (excluding Quebec)	Historical longitudinal cohort	Hospital attendance at transition	92	15–18 years versus 19–21 years	IP admissions	Mean per person per year	IRR Mean difference	Decreasing IP admissions
Levine et al.[60] (14)	Renal	USA	Multiple hospitals	X-section	Differences in healthcare use between children and adults	142	12–17 years versus 18–31 years	IP admissions ED visits Bed days	Model coefficients	IRR	Increase in IP admissions
Blinder et al.[61] (15)	Sickle cell	USA	5 states' routine records	X-section	Age-related treatment patterns	1113	>18 years versus ≤18 years (age range 0–50 overall)	OP attendances Total costs ED visits Bed days	Mean per person per year	IRR Mean difference	Increase in ED visits and bed days
Young et al.[63] (16)	Spina bifida	Canada	Ontario—routine records	X-section	Age-related treatment patterns	284	13–17 years (mean 15.3) versus 23–32 years (mean 26.3)	OP attendances IP admissions ED visits	Mean per person per year	IRR Mean difference	Decrease in IP admissions Increase in ED visits
Cohen et al.[54] (17)	Complex conditions	Canada	Ontario—routine records	Historical longitudinal cohort	Healthcare use at transition	2520	16–17 years versus 18–20 years	OP attendances IP admissions ED visits	Median per person per year	—	Increase in ED visits; decrease in IP admissions
Wijlaars et al.[55] (18)	Blood/cancer	United Kingdom	England—routine records	X-section	Emergency admissions across transition	Unknown (for blood/cancer disorders)	10–15 years versus 19–24 years	Emergency admissions	Mean per person per year	IRR Mean difference	Increase for females, decrease for males

Studies are ordered by condition and then publication date and numerical IDs provided in parentheses for each study are used consistently in tables and figures in this review (the included systematic review is not allocated an ID as it does not appear in other figures or tables).
OP outpatient, *IP* inpatient, *ED* Emergency Department, *IRR* incident rate ratio, *OR* odds ratio.

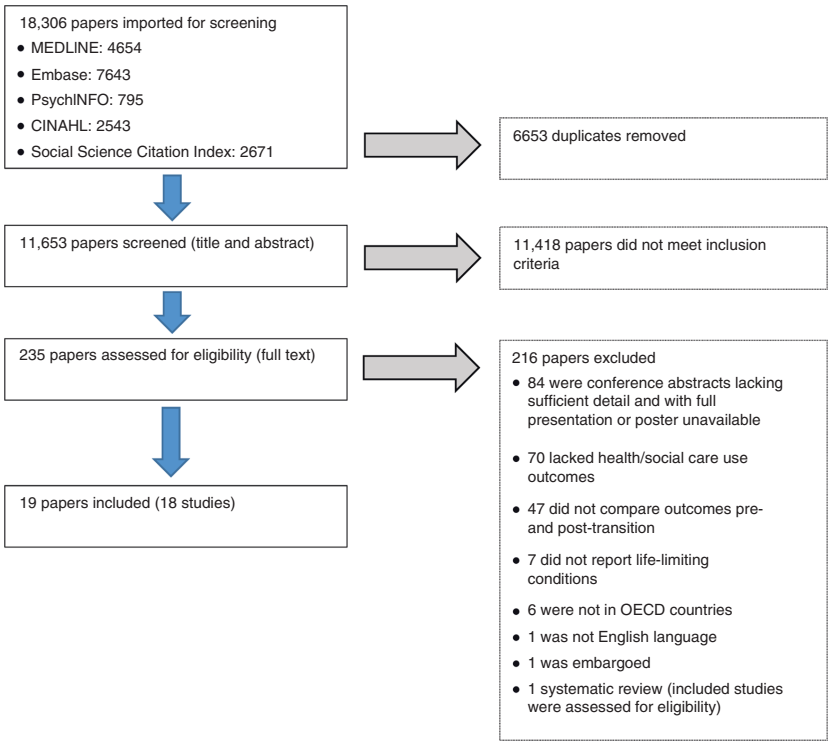

Fig. 1 PRISMA diagram for screening and study selection. Blue arrows show progression of papers between stages and grey arrows show papers rejected at each stage. Numbers are shown from each database and for each reason for rejection at full text eligibility assessment.

Inpatient bed days. Four studies looked at inpatient bed days. Three showed an increase and one a decrease (Fig. 3). Studies were of moderate quality (NOS = 3–5). *p* values were derivable for three studies and there was evidence for a decrease (Fisher's $p = 0.018$) and an increase (Fisher's $p = 0.002$).

Intravenous antibiotic courses. Three studies reported numbers of intravenous antibiotic courses, all showing an increase post-transition (Fig. 3). The studies were of moderate to high quality (NOS = 4–7). *p* values were derivable in two studies; there was no strong evidence for the observed increases (Fisher's $p = 0.103$).

Physiotherapy. Three studies reported percentages of individuals in receipt of physiotherapy, with two showing a decrease and one showing no change (Fig. 3). Study quality ranged from low to high (NOS = 2–7). *p* values were derivable for all studies and there was evidence of a decrease in provision of physiotherapy (Fisher's $p = 0.002$).

Costs. Only two studies reported differences in total healthcare costs, one showing lower and one higher costs post-transition (Fig. 3). Both studies were of moderate quality (NOS = 3–5). *p* values were derivable for both. A single study[61] that splits effects by receipt of iron chelation therapy is shown as two points in the albatross plot but as a single bar in the harvest plot. There was strong evidence of lower (Fisher's $p = 0.016$) and higher costs (Fisher's $p = 0.005$).

Other outcomes. One study[55] reported emergency admissions. This showed a significant increase for females post-transition and a significant decrease for males (Supplemental Table 1). This study was not included in the inpatient admission albatross plot due to a lack of information on sample size and omitted from the harvest plot because it could not be categorised as showing an increase or decrease (having subgroups showing both).

Another study[62] reported percentages of individuals in receipt of any HIV care and showed a decrease post-transition (Supplemental Table 1).

General Practitioner visits were reported in one study,[53] which showed that 72% of individuals visited post-transition and 68% pre-transition (odds ratio 1.2, 95% CI 0.3–4.5, Supplemental Table 1).

DISCUSSION

Summary of evidence

The included studies provide conflicting evidence on outpatient attendances, inpatient admissions, inpatient bed days and health service costs (for these outcomes, there was evidence for both increases and decreases post- versus pre-transition). There was greater consistency within countries than between them, where sufficient studies were available to gauge this. There was no evidence for changes in the numbers of intravenous antibiotic courses; there was evidence for both an increase in Emergency Department visits and a reduction in physiotherapy post- versus pre-transition.

Comparisons with other chronic conditions and implications for quality of care

Beyond LLC, for individuals with chronic conditions, there is evidence of disengagement and decreased outpatient attendance after transition.[15,32,68] This is particularly true for people with diabetes, where an increase in inpatient admissions is also

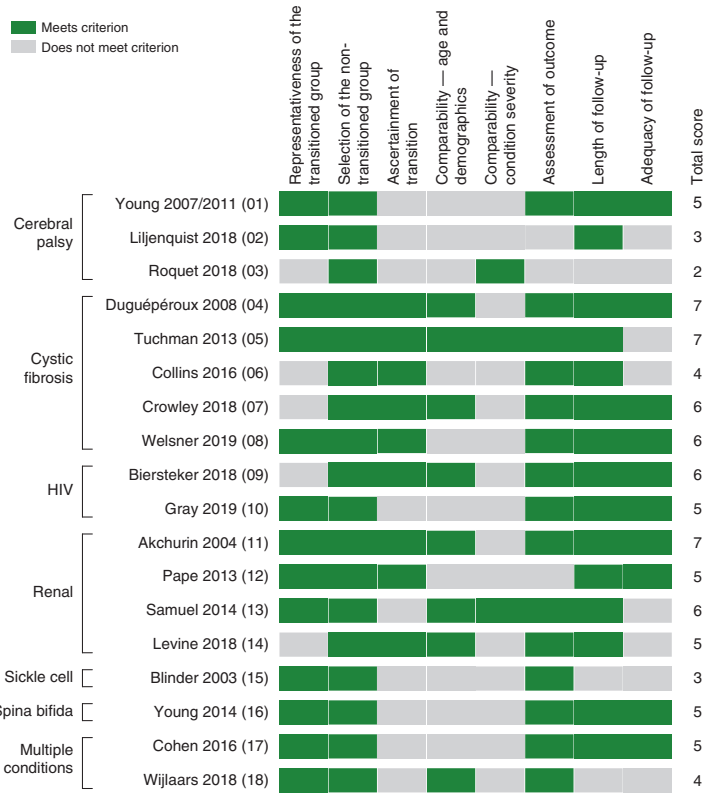

Fig. 2 Quality scores on modified Newcastle–Ottawa scale (see supplement for detailed scoring criteria). Green indicates that a point was scored on each criterion, grey indicates that it was not. Studies, with numerical IDs in parentheses, and conditions studied are indicated to the left and overall scores to the right.

observed,[69,70] although this varies with continuity of care.[71] The present review, however, reports a more mixed picture, with evidence emerging for both increased and decreased outpatient attendance. Disengagement may be driven by a perception that further care is unnecessary[72] and people with milder pre-transition sickle cell disease have lower transition success.[73] Disengagement may be less likely for people with a LLC due to the severity of their condition necessitating regular contact and due to many young adults with a LLC lacking capacity to decide whether they will or will not attend an appointment, this decision resting instead—as during childhood—with the carer. Implications for care may vary—changes in attendance may reflect different organisation of services post- compared to pre-transition, e.g. paediatrician visits where several different symptoms such as epilepsy and reflux were managed at once may be replaced with multiple outpatient visits to different specialists in adulthood. If either self-care (if appropriate) or primary care partly replace outpatient attendance after transition, the numbers of attendances may decrease. The studies did not report on the levels of attendance at outpatient appointments, which have been shown to be associated with use of emergency hospital care.[74]

The post-transition decrease in inpatient admissions for some included studies was unexpected—it is often anticipated that condition severity (and need for inpatient care) increases with age, independent of transition. However, planned admissions decrease after transition for a range of chronic conditions,[75] which may explain observed reductions in overall inpatient admissions in some included studies—most reported only overall admissions, not differentiating between emergency and planned. Increasing numbers of adults with chronic conditions are treated in children's hospitals,[76] which may suggest that suitable care is less available in adult inpatient settings or that transition is delayed for those most in need of inpatient care. An increase in emergency inpatient admissions post-transition may be indicative of worse condition management, but only one study looked at this and reported an increase for women but a decrease for men.[55]

For those with chronic conditions, Emergency Department visits are known to increase at transition ages,[77,78] and the limited evidence in this review is consistent with this. This may be linked to the transition, e.g. young people seeking hospital rather than primary care post-transition.[11,79] Alternatively, it may be due to natural progression of condition severity[80] or increased risk-taking behaviours at the age of transition[78] (those with long-term conditions are as likely as the those without long-term conditions to increase risk-taking behaviours at this age.[81]). Increases in Emergency Department visits are important as adverse care experiences may discourage future adult service engagement.[79]

Inpatient bed days depend on the combination of inpatient admissions and length of stay. Influences on the numbers of admissions discussed above are relevant—there are reasons to both expect more inpatient bed days (due to condition progression and potentially worse outpatient care) and fewer (due to fewer planned admissions[75] and potentially shorter stays in adult settings.[82])

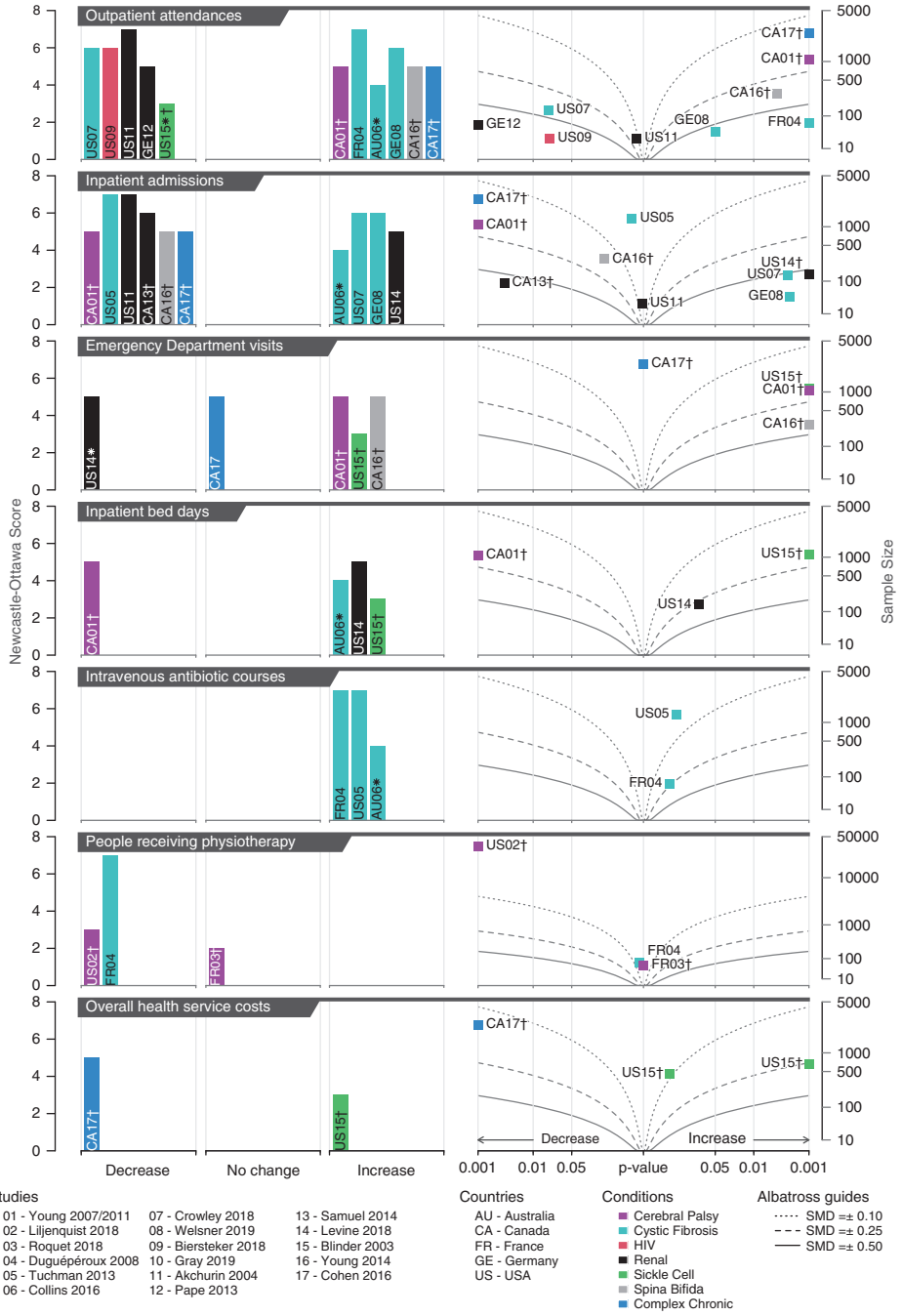

Fig. 3 Harvest plots (left) and albatross plots (right) for the indicated outcomes. Labels, e.g. CA-01, indicate country and numerical study ID. For albatross plots, *p* values < 0.001 are plotted at 0.001. Dagger (†) in the harvest and albatross plots indicates studies that did not provide justification for assignment to post- and pre-transition groups. In the harvest plots, asterisk (*) on a bar indicates a study not included on the corresponding albatross plot (as the *p* value could not be determined). Curved albatross guidelines are illustrative of the standardised mean difference (SMD) that would give rise to a given *p* value for a given sample size equally split between post- and pre-transition observation.

Reduced adherence to medications is observed in late adolescence and with the transition to adult services for many conditions.[83–85] Antibiotic use is particularly associated with cystic fibrosis to manage infection and is not necessarily indicative of worse outcomes.[86,87] However, the numbers of intravenous courses of antibiotics increased in the included studies post-transition and one study reported a fall in oral antibiotic use,[65] which may indicate worse condition management—oral antibiotics are preferred in the first instance.[88] Two of the included studies showed increases in home administration of antibiotics,[56,65] which may be appropriate but may indicate a lack of clinical oversight.

Lapses in physiotherapy after transition have long been identified as an issue for children with chronic conditions,[14,89] so support for this within the included studies is unsurprising. Increases in physiotherapy at home, either alone or with parents, as reported in one study[65] may be appropriate if sufficient training is given[90] but may also reflect a lack of service access.

Overall costs may reflect both differences in provider costs and differences in healthcare use. It has been shown that costs for adults admitted to children's hospitals are higher than for those treated in adult hospitals.[82] Increases may reflect more expensive emergency/hospital care rather than cheaper preventative care in the community or an outpatient setting.[91] Decreases in costs may indicate more efficient service delivery or reduced access to services. Reflecting this, the evidence on healthcare costs in the included studies was conflicting.

Variations between countries

Most countries (excepting the United States and Canada) had no more than two studies reporting the same outcome, so no conclusions could be drawn on differences between those countries. Studies from the United States and Canada showed opposite evidence on outpatient attendances (United States: decrease post- versus pre-transition; Canada: increase) and inpatient admissions (United States: increase; Canada: decrease).

Increased outpatient attendances may reflect organisational changes at transition, with multiple adult specialists replacing one paediatric specialist, particularly in Canada, where there are few multi-specialist clinics.[92,93] It may also reflect differences in funding and access, with Canada having a single-payer system while United States funding is a mix of public and private health insurance.[92] Insurance type has been associated with different healthcare use for children with a LLC[60] and adolescents with special healthcare needs are at higher risk of losing public insurance cover on reaching adulthood[94] (although insurance type has not been linked with transition success.[73]).

Differences in inpatient admissions may be due to differences in disease progression—survival times for cystic fibrosis are greater in Canada than in the United States.[95] They may also reflect differing demographics—it has been shown that some groups in the US have lower utilisation of outpatient services but higher inpatient use, irrespective of access to healthcare funding.[80]

The few studies looking at inpatient bed days aligned with those for inpatient admissions, with the Canadian study showing a reduction post-transition (despite reporting increased length of stay)[49,50] and the United States studies showing an increase.[60,61]

Variations between methods of ascertainment of transition

Results varied for some outcomes between studies that justified assignment of individuals to the post- or pre-transition groups and studies that did not. Misclassification may explain these differences but would be expected to result in smaller observed changes post- versus pre-transition (due to mixing of the groups) rather than the larger differences or apparent reversal of effect direction observed. Many of the studies not justifying assignment were from Canada and the observed differences largely reflect those between Canada and the United States. Country differences therefore seem more plausible than misclassification bias in explaining the observed variation. One Canadian study[54] justified assignment by stating that, apart from primary care, transition invariably happened by age 18 years, so other Canadian studies may have assigned post- and pre-transition groups correctly based on this age cut-off, despite not justifying this.

Variations between conditions

Comparisons between conditions were limited as few conditions had more than two studies reporting the same outcome. Cystic fibrosis studies more commonly reported increases in healthcare use post-transition than decreases—cystic fibrosis has well-established transition programmes aimed at maintaining engagement.[87] The reverse was true for renal conditions, for which studies were largely concerned with paediatric transplant recipients, where many problems have been identified with transition and ongoing engagement in care.[96]

Contribution of this review

The existing systematic review on healthcare use[51] had a narrower focus than the present review, including only studies on cystic fibrosis. It found no significant differences in the number of antibiotic therapies and hospital attendance, but an increase in outpatient appointments. The included papers reporting these outcomes were also included in the present study.

The present review is the first to assess evidence across a range of LLCs. It reveals conflicting evidence, some of it patterned by country, suggestive of different healthcare regimes delivering different changes at transition. It finds that assessments of changes in healthcare use at the transition have been inconsistent, with many different outcome measures, designs and methods of ascertaining transition. It highlights the need for more high-quality research in this area.

Limitations

Included studies. As demonstrated by the NOSs, quality of the included studies varied. Half failed to determine whether individuals were in paediatric or adult care, instead using a simple age cut-off. This was appropriate to the research questions of some studies, but a limitation for the review due to potential misclassification bias.

Most studies failed to separate possible effects of transition, age and condition severity. Only one study[56] propensity-score matched post and pre-transition groups and two[53,66] controlled for condition severity. The majority did not control for age, so may have measured effects associated with age and condition progression, rather than transition. There is a need for research that separates associations with age from associations with receipt of either paediatric or adult care.

Differences in age ranges of compared groups limited comparability between studies and were one reason a meta-analysis was not conducted. This reflected differences in the age at which transition takes place, both between and within countries.[15,18,51] Many studies used means and standard deviations to summarise event counts, even though these were likely to be highly skewed, following a Poisson or negative-binomial distribution. Outcomes measured varied greatly, as observed in reviews of transition for chronic conditions,[18,51,97] limiting comparability.

Finally, the included studies were concentrated on only a small number of the more common LLCs. In particular, neurological conditions, affecting 12% of children with a LLC[1] and one of the largest groups referred for paediatric palliative care,[98,99] were under-represented. The generalisability of findings across LLCs as a whole is therefore questionable.

Review limitations. The study limitations prevented a meta-analysis or other effect-size pooling. The synthesis used was appropriate[29] but explored directions of effect and

strength of evidence; no conclusions could be drawn on effect size.

There is no definitive list of LLCs and whether a condition is included can depend on severity (e.g. cerebral palsy). Study inclusion in this review depended on the authors' judgement, based on previous work developing lists of LLCs.[1] Other reviewers might come to different decisions on some studies. Presentation of the results categorised by condition does, however, aid the reader in gauging what effect excluding, for example, cerebral palsy or sickle cell disease would have.

Transition is not always clearly defined, even at the individual level, with some adults continuing to receive some care in paediatric settings. However, the transition is experienced as a very real phenomenon by young people and their families.[6,9,10,13] Definitions used in many of the studies were based on well-defined cut-offs, such as transfer from a paediatric to an adult clinic.

The search strategy for this review extended previously developed search strategies and was designed to maximise sensitivity. Although initial title and abstract screening was done by one reviewer (with 20% checked by a second reviewer), full-text review was carried out by two reviewers independently. There is a risk of missed relevant studies among the 80% of titles and abstracts screened by only one reviewer,[100,101] but in the 20% of titles and abstracts that were screened by a second reviewer, no studies rejected by the first reviewer were ultimately included in the review.

Eighty-four conference abstracts were excluded due to the full presentation or poster being unavailable. One study (a doctoral thesis[102]) was excluded as the full text was embargoed. It is possible that inclusion of these, had full-text been available, would have altered conclusions.

Future research

There has been widespread recognition of the need for improvement of the transition and suggestions of how his might be done.[18,19,91,103] However, more high-quality research is needed that analyses healthcare use across the full range of LLCs to better target interventions with potential to be cost-effective. In particular, the present research in this area is lacking in the following areas:

- possible misclassification bias due to poor ascertainment of transition;
- inconsistent and sometimes inappropriate outcome measurements, e.g. the use of mean values to describe highly skewed distributions;
- a lack of control for potential confounders, particularly increasing severity of condition with increasing age, irrespective of transition status.

Research is needed that more directly links transition and healthcare use, through analysis of the time periods immediately before and after transition and the use of methods enabling causal inference.

CONCLUSIONS

The evidence on changes in healthcare use post- versus pre-transition from paediatric to adult healthcare is mixed and conflicting. There is some evidence of an increase in Emergency Department visits and a reduction in access to physiotherapy but different patterns were identified for outpatient attendances and inpatient admissions between the United States and Canada. This may be linked to differences in organisation and funding of healthcare services, and in at least some populations, significant changes in healthcare use were observed at the transition.

More high-quality research is needed to provide a stronger evidence base for the extent to which widely reported concerns about the transition are reflected in changes in healthcare use and resource utilisation.

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AUTHOR CONTRIBUTIONS

S.W.J. conceptualised and designed the study, designed and conducted the searches and screening, extracted data, reviewed study quality, drafted the initial manuscript, reviewed and revised the manuscript and gave final approval of the version to be published. D.R. contributed to the design of the study, conducted the screening, reviewed and revised the manuscript and gave final approval of the version to be published. K.F. contributed to the design of the study, the design of the searches and choice of databases searched, reviewed and revised the manuscript and gave final approval of the version to be published. G.R. helped conceptualise the study, contributed to the design of the study, reviewed and revised the manuscript and gave final approval of the version to be published. L.K.F. helped conceptualise the study, contributed to the design of the study, the design of searches and choice of databases searched, screening, reviewed and revised the manuscript and gave final approval of the version to be published.

ADDITIONAL INFORMATION

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A1.3 Paper 3: Estimation of age of transition from paediatric to adult healthcare for young people with long term conditions using linked routinely collected healthcare data

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Please see Section 9.3 for discussion of other relevant issues identified since publication of this paper.

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Estimation of age of transition from paediatric to adult healthcare for young people with long term conditions using linked routinely collected healthcare data

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Abstract

Introduction
Healthcare transitions, including from paediatric to adult services, can be disruptive and cause a lack of continuity in care. Existing research on the paediatric-adult healthcare transition often uses a simple age cut-off to assign transition status. This risks misclassification bias, reducing observed changes at transition (adults are included in the paediatric group and vice versa) possibly to differing extents between groups that transition at different ages.

Objective
To develop and assess methods for estimating the transition point from paediatric to adult healthcare from routine healthcare records.

Methods
A retrospective cohort of young people (12 to 23 years) with long term conditions was constructed from linked primary and secondary care data in England. Inpatient and outpatient records were classified as paediatric or adult based on treatment and clinician specialities. Transition point was estimated using three methods based on record classification (First Adult: the date of first adult record; Last Paediatric: date of last paediatric record; Fitted: a date determined by statistical fitting). Estimated transition age was compared between methods. A simulation explored impacts of estimation approaches compared to a simple age cut-off when assessing associations between transition status and healthcare events.

Results
Simulations showed using an age-based cut-off at 16 or 18 years as transition point, common in research on transition, may underestimate transition-associated changes. Many health records for those aged <14 years were classified as adult, limiting utility of the First Adult approach. The Last Paediatric approach is least sensitive to this possible misclassification and may best reflect experience of the transition.

Conclusions
Estimating transition point from routine healthcare data is possible and offers advantages over a simple age cut-off. These methods, adapted as necessary for data from other countries, should be used to reduce risk of misclassification bias in studies of transition in nationally representative data.

Keywords
transition (to adult care); life-limiting conditions; chronic conditions; routine healthcare data

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Introduction

There are many inevitable health and healthcare related transitions: between treatments, from hospital to home or - for the elderly - to nursing care. Transitions have the potential to be disruptive, result in discontinuities in care and increase the burden on those receiving care, their families and carers [1–4].

The transition from paediatric to adult healthcare has been an area of research and policy interest in recent years [5–16]. This transition is likely to be most noticeable to children with long term conditions with frequent use of outpatient or inpatient services, for whom there is likely to be a change in ward visited and clinical staff seen [17, 18]. There are many concerns around the impact of this transition - including a lack of continuity in care, lack of familiarity among adult specialists with some of the health conditions and personal histories of the young people and potential gaps in services, such as physiotherapy, that were provided continuously during childhood [17, 18].

A large body of research on the impacts of transition from paediatric to adult healthcare exists, including multiple systematic reviews, but has limitations due to difficulties in determining when children transition. Age at transition, although typically from age 16 to 19 years in the United Kingdom [17] and planned to be around age 18 years in the United States, [19] can vary widely, depending on health condition, severity and the availability and remit of local services [17, 20, 21]. Existing studies fall into two main types: (i) small studies from individual (or a small cluster of) clinics or insurance claims data [22] and (ii) population data studies [20, 23].

Small, clinic based studies have the advantage that they normally have data to identify the point of transition for each individual, for example by using the date of leaving (paediatric clinics) or date of joining (adult clinics) [20]. Insurance databases may contain similar data [22]. However, these studies may not be representative of the population of interest. For example, geographical variations, specialism in a subset of conditions or – particularly in healthcare systems that are not single-payer – differences in the socioeconomic status of individuals attending different clinics or covered by different insurers, may limit generalisability.

Large-scale population studies, using routinely collected data, can be nationally representative and have large samples [24, 25]. However, they often lack data on when individuals transition, so most studies use a simple age cut-off and the actual age of transition may not be reported at all [26]. This approach risks misclassification bias, which may lead to underestimation of any measured change at transition as the post-transition group includes individuals pre-transition and vice versa [27, 28]. There may be systematic bias, e.g. between health conditions or socio-demographic groups, if transition age varies between these groups [21]. There have been attempts to use data to identify paediatric and adult care providers, but these approaches lack validation and may only be feasible in countries where these data are explicitly collected [20, 21, 29–31].

The evidence base for the impact of transition from paediatric to adult health services would benefit from combining the scale and representativeness of routine data population studies with the ability of small studies to accurately determine transition point. This would enable better quality research into potential issues at transition. It would also enable evaluation of changes in service provision at transition using routine health data - changes in policy or service delivery are rarely evaluated before implementation, but could be evaluated retrospectively [32–35].

This study aimed to determine the feasibility and implications of estimation of transition age from routinely collected health data. It had these specific objectives:

- Define a classification system for inpatient and outpatient records as paediatric, adult or unknown within a national healthcare dataset
- Develop and apply methods of estimating the transition point from these data
- Compare estimations of transition age from these methods
- Assess implications of using estimated transition ages when studying differences in pre- and post-transition outcomes, through simulated data

Methods

Ethical approval

The study was covered by general ethical approval (ref: 05/MRE04/87) for studies using Clinical Practice Research Datalink (CPRD) data for observational research approved by its Independent Scientific Advisory Committee (ISAC). This study was approved by ISAC (protocol ref: 19_215R).

Patient and public involvement

The Martin House Research Centre Family Advisory Board [36] was consulted before beginning this work, to understand how transition is experienced by families of children with life-limiting conditions and after completion of initial analyses to discuss the estimation methods used and the findings. This informed the choice of estimation methods used and the recommendation of a preferred estimation method (see Discussion).

Datasets

Data from the CPRD dataset were used. The CPRD is a research dataset using records from primary care practices in England, chosen to provide a nationally representative sample of the population [37]. The CPRD offers different datasets based on records from different primary care database providers; in this study, GOLD data were requested. Primary care data (2000-2018), Hospital Episode Statistics (HES) [25] Admitted Patient Care (APC, 2000-2018), Outpatient (2000-2018) and Accident and Emergency (A&E, 2007-2018) records were requested from CPRD for individuals aged 12-23 years of age at any point from 1 January 2000 to 31 December 2018. CPRD linked the datasets using NHS number, sex, date of birth and postcode [37].

Identification of long term conditions

Read codes (in primary care records) and *International Classification of Diseases 10th Revision* (ICD-10) (in inpatient and outpatient records) [38] were used to identify chronic and life-limiting conditions using previously developed coding frameworks [39–41] (also available from the corresponding author on request). Chronic conditions were identified using a previously developed coding framework in which chronic conditions were defined as any health problem likely (i.e. in more than 50% of cases) to require follow-up (hospital admissions, outpatient visits, medications) for more than one year [41, 42] (also available from the corresponding author on request). Life-limiting conditions included conditions that shorten life, such as Duchenne Muscular Dystrophy, and conditions that threaten to shorten life, but may be cured, such as cancer [43]. The subdivision was used due to expected differences in care patterns - i.e. those with life-limiting conditions may have more outpatient contact and inpatient admissions as children and would experience a noticeable transition from paediatric to adult care and may transition later; some of those with non-life-limiting chronic conditions may have less outpatient contact and/or fewer inpatient admissions.

Cohort identification and sub-groups

A retrospective cohort was constructed including all children and young people who satisfied all of the following criteria:

1. Had a life-limiting or other chronic condition recorded aged 12 to 23 years
2. Were present in the CPRD dataset from at least 15 to 20 years of age
3. Were no older than 15 years in 2007

Presence from age 15 to 20 years was required to make it likely there would be at least one year of records either side of transition, expected to commonly be from 16 to 19 years. Individuals might leave the dataset before age 20 years for a variety of reasons, including moving GP practice or death. A maximum age of 15 years in 2007 was required to make it likely that there would be childhood records classified as paediatric (most paediatric specialty codes were not present before 2007, as detailed below). Diagnoses recorded before age 12 years but never recorded again in ages 12-23 years were considered not relevant (either misdiagnoses, or conditions that had resolved). Individuals with any diagnoses in the life-limiting condition coding frameworks were assigned to a life-limiting condition group; individuals with a diagnosis matching a chronic condition were assigned to the chronic condition group. The condition groups were hierarchical: those with both life-limiting and chronic diagnoses were assigned to the life-limiting group. Individuals entered the cohort at age 12 years or, if later, at first appearance in the CPRD data; they left at age 23 or, if earlier, on leaving the CPRD dataset. (Figure 1).

A subgroup was defined to include individuals with at least one secondary care record (inpatient or outpatient) in each year when aged 15 to 20 years - i.e. a group with frequent inpatient and/or outpatient appointments in the years in which transition was expected to take place. This group should have more data to estimate transition and be likely to feel the impacts of transition more strongly due to having a change in provider of regular hospital care. This groups is hereinafter referred to as the "Frequent Care group".

Data management

Data were managed using Microsoft SQL Server 2019.

Sex and year of birth were provided in CPRD data. Deprivation category (split into five groups from 1 - least deprived to 5 most deprived, using the Index of Multiple Deprivation 2010, based on the last known address of the individual [44]) was provided as linked data. Ethnic group (11 categories: Black African, Black Caribbean, Black Other, Chinese, Bangladeshi, Indian, Pakistani, Other Asian, White, Mixed or Other [45]) was recorded in the linked HES data, based on the census groups [45]. If an individual had more than one ethnic group recorded, it was set by CPRD to the most commonly recorded group, excluding unknown [37].

Estimation of transition point

Classification of care records as paediatric or adult

The estimation of a transition point from routine healthcare records requires the classification of records as either paediatric or adult. This information is not always explicit in the routine healthcare records, but both inpatient and outpatient records record the "treatment specialty" (the specialty under which treatment was provided) and the main specialty of the consultant in charge of care. These specialties are largely split into paediatric and adult groups from 2006/07 onwards, when a number of paediatric specialties were introduced [46].

Treatment and main consultant specialities were split into three categories: paediatric, adult and unclassified. This was initially based on specialty descriptions, then refined with some adult classifications being moved to undefined where, at the judgement of the authors, (i) the treatment specialty was unlikely to be the most common specialty for many individuals (e.g. Ear, Nose and Throat) and (ii) the specialty was frequently observed for children at ages under 14 years of age, which were considered unlikely to represent adult care [17].

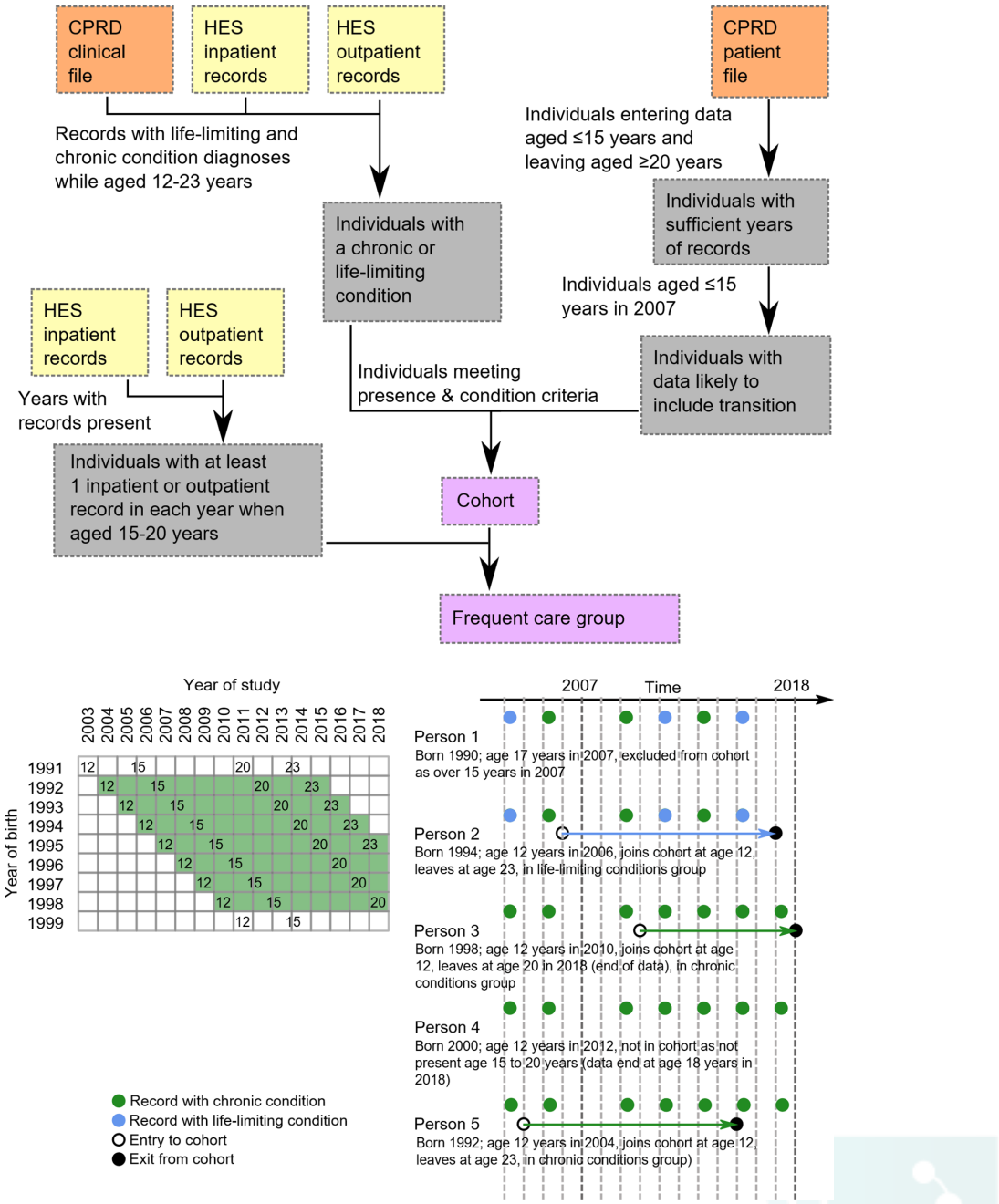
Classification of treatment and consultant main specialties as paediatric, adult or undefined is detailed in Supplementary Tables 1 and 2.

Approaches to estimating a transition point

Three main approaches were used to estimate transition age, with reference to suggestions identified in the literature [20] and following discussions with the Martin House Research Centre Family Advisory Board. These were:

- Setting the transition point as the last paediatric record (the "Last Paediatric" method)
- Setting the transition point as the first adult care record (the "First Adult" method)
- Setting the transition point such that it minimised the number of earlier records that were classified as adult and the number of later records that were classified as paediatric (the "Fitted" method)

Figure 1: Cohort construction



Top: flow diagram showing use of primary care (CPRD) and hospital (HES) datasets. Bottom-left: matrix of year of birth versus study year, showing when individuals born in each year are potentially eligible (depending on diagnoses and continued presence in CRPD data) for cohort inclusion (green shading). Individuals must be aged 12–23 years, present from at least 15–20 years and no older than 15 years in 2007. Numbers in boxes indicate age in year. Bottom-right: example scenarios for inclusion and exclusion, including allocation to condition groups.

Alternative approaches requiring a minimum number of adult records to be recorded to determine transition [20] were rejected as it was felt that these would discriminate between those with more and less frequent healthcare use (for example, if three adult records were required, a young person with three or more outpatient appointments each year would be

judged to transition earlier than one with only one outpatient appointment each year, even if both transitioned at the same time).

The First Adult and Last Paediatric approaches are self-explanatory. For the Fitted approach, if an individual had N records in ascending date order then for each record, j (where $j = 1, \ldots, N$), the following calculation was made, in which *paed* is 1 for a record classified as paediatric and 0 otherwise and *adult* is 1 for a record classified as adult and 0 otherwise:

$$Transition\ score_j = \frac{\sum_{i=1}^{i=j-1} paed_i + \sum_{i=j+1}^{i=N} adult_i}{N-1}$$

The transition point was the record with highest transition score. If there were ties then the mean date of the tied records was taken as the transition point.

In the event of a clear-cut transition, in which an individual had all records up to a point classified as paediatric and all records after that point classified as adult, the three methods are closely equivalent; differences become greater when there are either early or late records classified as adult or paediatric, respectively (Figure 2).

In all approaches, individuals had to have at least one paediatric and at least one adult record to have a transition point estimated. Individuals were then classified as in paediatric care in years before the year containing the transition point and in adult care in the year containing the transition point and later years (this on the basis that any disruption from transition to adult care begins with the transition) [12, 13, 17, 18].

Analyses

Cohort characteristics

The numbers of individuals in the cohort and in each sub-group were calculated and summarised graphically.

Record classification

The classification of records as either paediatric or adult was summarised by age and split by condition group and inpatient admissions and outpatient appointments.

Ability to estimate transition

The percentage of individuals in the cohort for whom a transition point could be determined (i.e. had at least one paediatric and one adult record) was calculated, for the whole cohort and the Frequent Care group, by year of birth.

Estimation of transition point

Age at transition was estimated for the whole cohort and the Frequent Care group, under the methods outlined above. These were presented graphically by method and density distributions of differences in transition age were compared pairwise between methods. Individuals for whom a transition point could not be estimated were excluded.

Impacts of estimating transition age from the data

Finally, a simulation was used to understand the possible impact of using different methods to estimate transition on an outcome that varied between paediatric and adult care.

Many healthcare outcomes of interest - for example, numbers of A&E visits, inpatient admissions, GP consultations or inpatient bed days are count data. Poisson distributions were used in the simulations as the source of notional outcome data pre- and post-transition, assumed to be counts of a healthcare event. A negative binomial distribution may be more realistic in many circumstances, to account for over dispersion, but adds complication by requiring not only specification of means for the pre- and post-transition distributions, but also their dispersion [47] The pre-transition Poisson distribution mean was set to 2 (as a realistic mean for a healthcare event - GP consultations - in the population [48]) and the post-transition Poisson distribution mean was set to 2.4 (20% higher - clinically significant and also plausible at post-transition ages for GP consultations [48]).

Individuals in the cohort were each assigned five binary transition variables in each year, with 1 indicating adult and 0 indicating child, as follows:

i. 0 in years prior to transition year as estimated by the Last Paediatric estimation method and 1 otherwise

ii. 0 in years prior to transition year as estimated by the First Adult estimation method and 1 otherwise

iii. 0 in years prior to transition year as estimated by the Fitted estimation method and 1 otherwise

iv. 0 in years prior to reaching age 16 years and 1 otherwise (i.e. transition set to age 16 years)

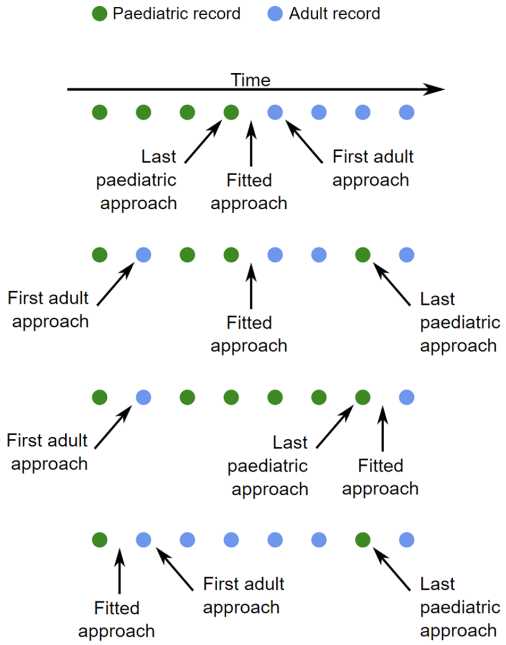
v. 0 in years prior to reaching age 18 years and 1 otherwise (i.e. transition set to age 18 years)

Three outcome variables were assigned each year, one for each of the transition estimation methods. These were populated with counts drawn at random from the pre-transition Poisson distribution if the corresponding transition variable was 0 for that year and drawn from the post-transition distribution if the corresponding transition variable was 1 for that year (Table 1).

Poisson regressions were then used to estimate associations between the count outcomes and the binary transition indicators, using only observations while aged 12 to 23 years and from the final two years of paediatric care and the first two years of adult care (as defined by the transition method used to assign outcomes - e.g. when comparing against the Last Paediatric method, years 2009–2012 would be used in Table 1). Used observations were restricted to this four year window as being of the most interest for identifying changes at transition (for example, data from ages 12 and 20 years might be of little interest for assessing impacts of a transition occurring at age 16 years, but data from ages 14, 15, 16 and 17 years would be more relevant). For each of the three outcome variables, five regressions were run, one each for each of the binary transition variables.

Individuals for whom a transition point could not be estimated were excluded from the simulation.

Figure 2: Estimation of transition points under different patterns of records (inpatient and outpatient) classified as paediatric or adult



For simplicity, no unclassified records are shown, as these do not influence estimation of transition point.

Table 1: Example (dummy) data for the simulation

Year	Age	$Trans_{FA}$	$Trans_{LP}$	$Trans_{Fit}$	$Trans_{16}$	$Trans_{18}$	$Outcome_{FA}$	$Outcome_{LP}$	$Outcome_{Fit}$
2006	14	0	0	0	0	0	$P_{2.0}$	$P_{2.0}$	$P_{2.0}$
2007	15	**1**	0	0	0	0	$\mathbf{P_{2.4}}$	$P_{2.0}$	$P_{2.0}$
2008	16	**1**	0	0	**1**	0	$\mathbf{P_{2.4}}$	$P_{2.0}$	$P_{2.0}$
2009	17	**1**	0	**1**	**1**	0	$\mathbf{P_{2.4}}$	$P_{2.0}$	$\mathbf{P_{2.4}}$
2010	18	**1**	0	**1**	**1**	**1**	$\mathbf{P_{2.4}}$	$P_{2.0}$	$\mathbf{P_{2.4}}$
2011	19	**1**	**1**	**1**	**1**	**1**	$\mathbf{P_{2.4}}$	$\mathbf{P_{2.4}}$	$\mathbf{P_{2.4}}$
2012	20	**1**	**1**	**1**	**1**	**1**	$\mathbf{P_{2.4}}$	$\mathbf{P_{2.4}}$	$\mathbf{P_{2.4}}$
2013	21	**1**	**1**	**1**	**1**	**1**	$\mathbf{P_{2.4}}$	$\mathbf{P_{2.4}}$	$\mathbf{P_{2.4}}$

Data are shown for a single individual, present from 2006 to 2013 aged 14 to 21 years. In each year the person has five binary transition variables, for the three estimation methods and transition set to age 16 and age 18 years. For this person, the First Adult approach estimates transition at 15 years, Last Paediatric approach estimates transition at 19 years and Fitted approach estimates transition at 17 years - indicated by 0 for paediatric care and 1 for adult care in the $Trans_{FA}$, $Trans_{LP}$ and $Trans_{Fit}$ variables, respectively. The three outcome variables have values drawn from the pre-transition Poisson distribution ($P_{2.0}$) where the corresponding transition variable is 0 and from the post-transition distribution ($P_{2.4}$) where the corresponding transition variable is 1. As a visual guide, post-transition observations are in bold type.

The sets of models were stratified by demographic variables (sex, deprivation category and ethnic group - the last collapsed to White and non-White due to small numbers) and condition group to explore the potential for systematic bias in using a fixed transition age. The Frequent Care group was also included as a sub group.

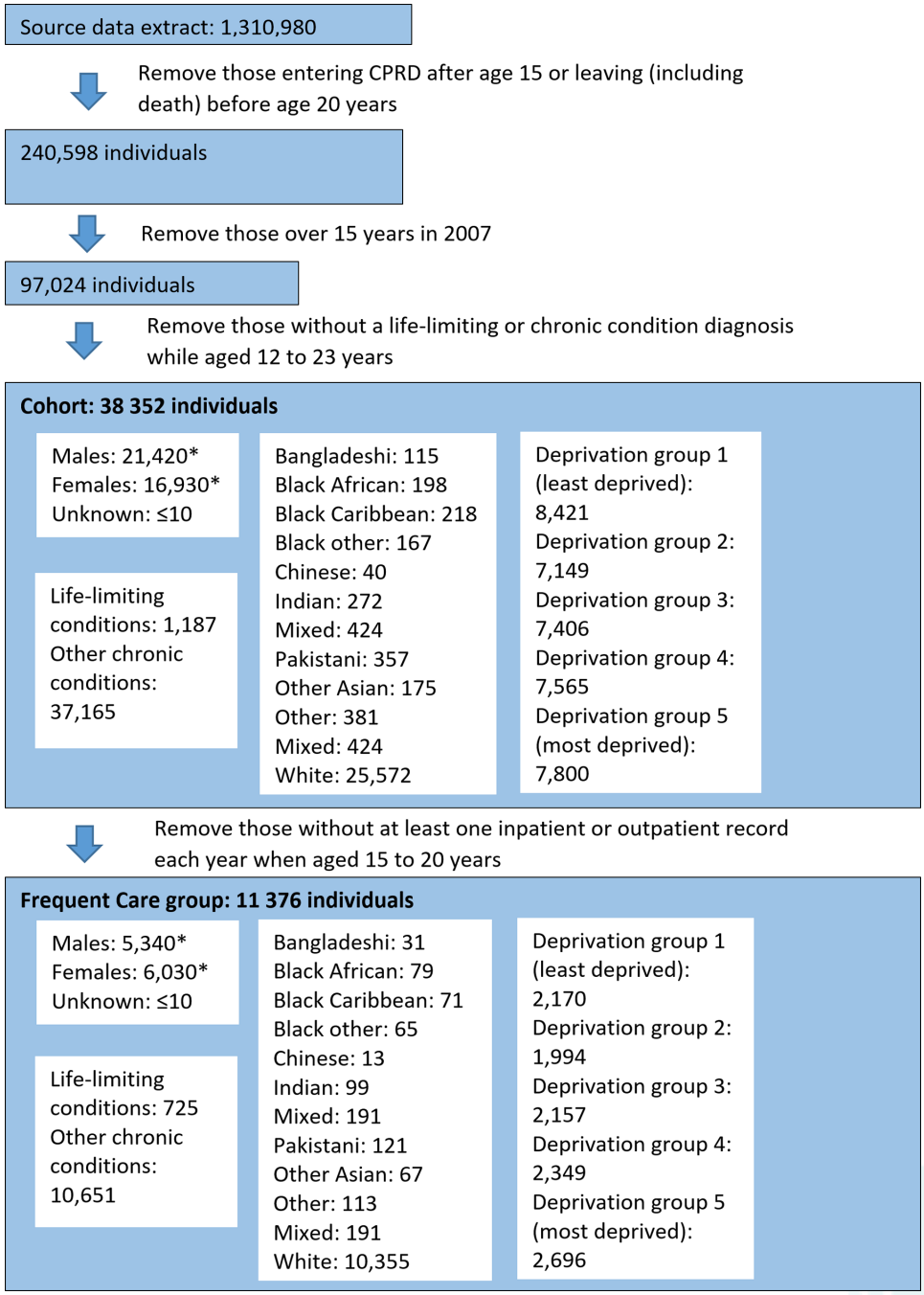
The process described above was repeated 10,000 times (with random draws each time from the appropriate Poisson distributions). The change in predicted events associated with transition according to the models was calculated as the mean across the 10,000 runs and the 95% confidence interval as the 2.5 and 97.5 percentiles.

Results

Cohort summary

There were 38,352 individuals in the data who met the inclusion criteria (Figure 3); 1,187 with life-limiting conditions and 37,165 without life-limiting conditions but with other

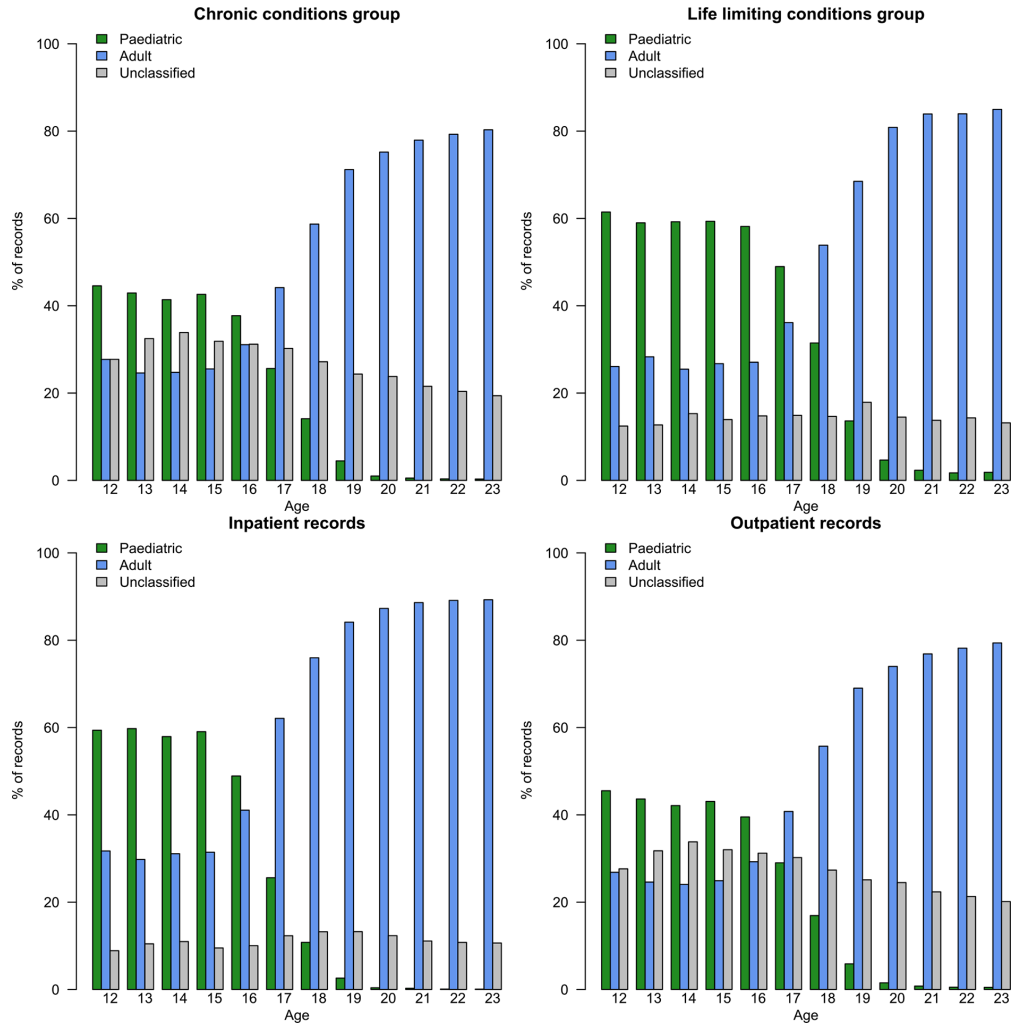
Figure 3: Cohort construction flow diagram showing inclusion criteria and data sources, with final sizes of cohort, Frequent Care group and the demographics in those groups



* indicates figures rounded to the nearest 10 to prevent disclosure of exact numbers with missing data.

chronic conditions. 106 individuals who were eligible on other criteria were excluded due to death (and so leaving the dataset before age 20 years). Of these, 57 had chronic conditions recorded and 49 had life-limiting conditions recorded. 11376 had at least one inpatient or outpatient record in every year aged 15 to 20 years (Frequent Care group). 61% of young people in the cohort with a life-limiting condition were also in the Frequent Care group, compared to only 29% of cohort

Figure 4: Percentages of records classified as paediatric, adult or unclassified by age in the chronic conditions group (inpatient and outpatient records), the life-limiting conditions group (inpatient and outpatient records), among inpatient records (whole cohort) and among outpatient records (whole cohort)



members with chronic conditions. There were more males than females in the cohort, but fewer males than females in the Frequent Care group. There were many cohort members with unknown ethnic group (27%) mainly due to these individuals lacking hospital records (the source of ethnic group data). In the Frequent Care group, with - by definition - hospital records, under 2% had unknown ethnic group. At least 67% of the whole cohort were known to be White; among those of known ethnic group 92% were White. The least deprived group was largest in the cohort, but the most deprived group was largest in the Frequent Care group.

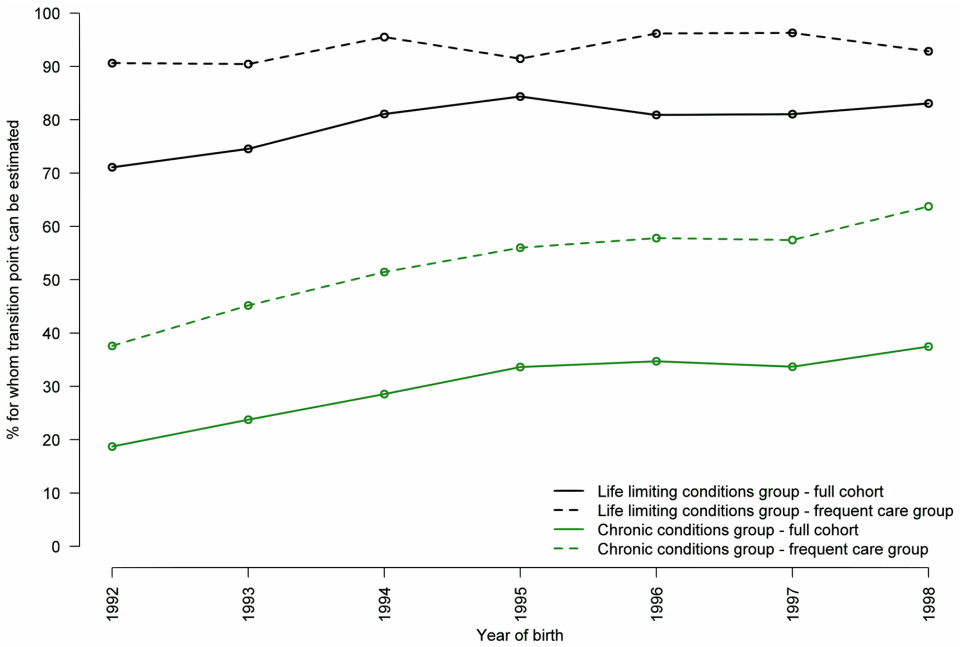
Record classification

The classification of cohort member records is illustrated in Figure 4. Few records beyond age 19 years are classified as paediatric (although more in the life-limiting conditions group than in the chronic conditions group). Many records are classified as adult below 16 years of age (8% of all adult classifications were in records aged under 16 years). Inpatient records are more likely than outpatient records to be classified as paediatric below age 16 years, but make up only 14% of the total number of records.

Ability to estimate transition

The percentage of individuals for whom transition can be estimated (those with at least one paediatric record and at least one adult record) is illustrated in Figure 5. Transition can be estimated for more of those with life-limiting conditions than with chronic conditions and particularly so in the Frequent Care group - e.g. 93% of those with life-limiting

Figure 5: Proportions of children and young people for whom transition point can be estimated (i.e. the proportion having both paediatric and adult records)



Split into chronic conditions and life-limiting conditions groups and further by whole cohort and Frequent Care group. Year of birth is limited to 1992 to 1998 as this defines the cohort (those born before 1992 were older than 15 years in 2007 and those born after 1998 had not reached 20 years in 2018 when the data end).

conditions in the Frequent Care group born in 1998 had an estimated transition point compared to 83% of those with life-limiting conditions in the whole cohort; for those with chronic conditions, corresponding figures are 64% (Frequent Care Group) and 37% (whole cohort).

Estimation of transition point

Estimation methods are compared in Figure 6, for the whole cohort and Frequent Care group. Major differences for the whole cohort compared to the Frequent Care group are the higher number of late transitions (age 20 years or higher) when the First Adult approach is used and higher number of early transitions (age 13 years or lower) when the Last Paediatric approach is used. The First Adult approach estimates a large number (>20%) of early transitions for both the whole cohort and the Frequent Care group.

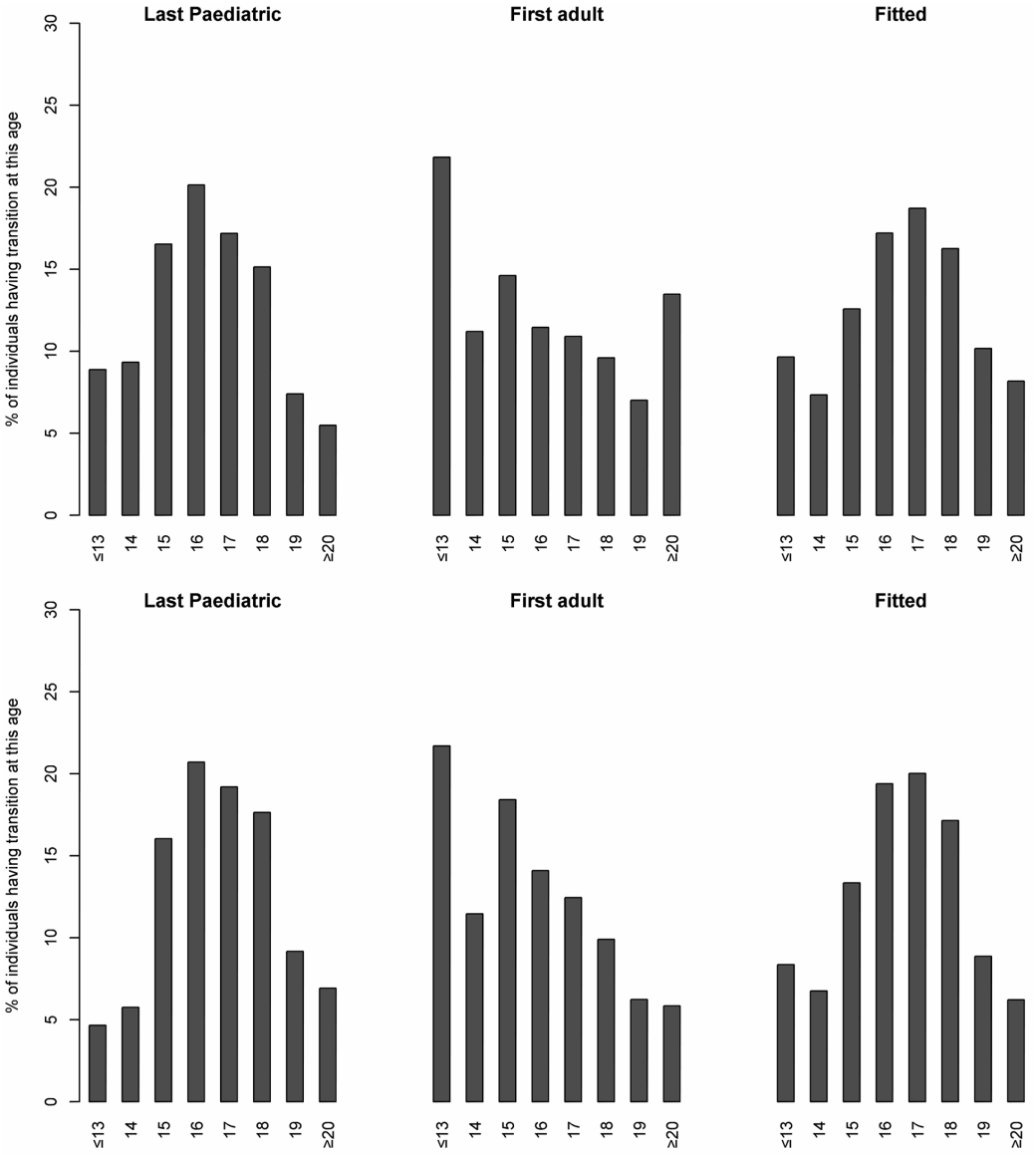
Distributions of differences in transition age estimated by the different methods are illustrated in Figure 7. Agreement between estimation methods is greater for the Frequent Care group than for the whole cohort (narrower distributions around 0 and a higher central peak close to 0), particularly when comparing the Last Paediatric and Fitted approaches. The Last Paediatric and Fitted approaches agree more closely than either do with the Last Adult approach.

Impacts of estimating transition point from the data

The results of the simulation, illustrating the potential impact of using the transition estimation methods set out above compared to a simple age cut-off at 16 or 18 years, are shown in Figure 8. Each panel shows the change in outcome event counts associated with transition for each of the methods with one of the estimation methods set as the 'true' transition (i.e. the outcome variable associated with that transition method is used - in Table 1, if the Last Paediatric approach is used as 'true' transition then $Outcome_{LP}$ is used as the dependent variable in the regressions). Using a transition estimation method other than the one set as the 'true' transition point (e.g. using, from Table 1 $Trans_{FA}$ as independent variable with $Outcome_{LP}$ as dependent variable) results in underestimation of the transition effect. Depending on the estimate used as 'true' transition, use of a simple age cut-off underestimates the effect of transition by 70% or more in many cases. The Last Paediatric and Fitted Approaches underestimate by around 50–60% compared to each other. The First Adult Approach shows greatest underestimation compared to the Last Paediatric approach (75% or greater reductions).

There is little evidence of differential bias between methods in sub groups of the cohort - underestimation is broadly similar between groups, at least within the confidence intervals with the studied data. However, the sample size in sub groups may be underpowered to detect any differences.

Figure 6: Distributions of age at transition points estimated using the three methods as a percentage of all individuals in the whole cohort (top panel) or Frequent Care group (lower panel)

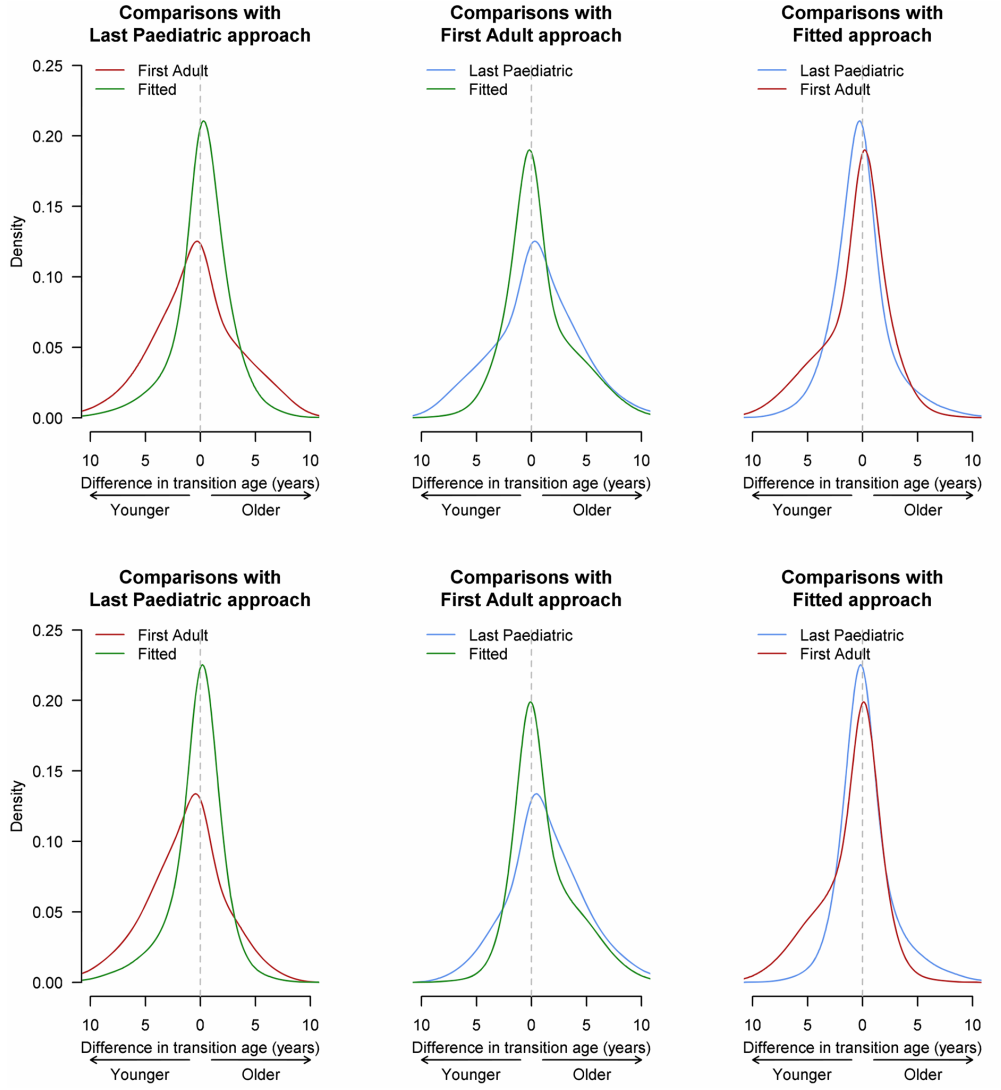


Discussion

This study shows that the estimation of point of transition from paediatric to adult healthcare is feasible using national healthcare data from England. Estimating transition points from the data has advantages over using a simple age cut-off as it can provide greater sensitivity - the simulation shows that use of a simple age cut-off to assign transition status has the potential to markedly underestimate the association between transition status and an outcome, reducing point estimates of effect size by, in some cases, 70% or more. This is important for studying adverse outcomes associated with transition (e.g. increases in emergency inpatient admissions or A&E visits at transition) to help target interventions and also enables better differentiation between alternative care pathways in evaluations of interventions and policy changes.

Although transition estimation is feasible in many cases, for some individuals transition estimation is limited by an inability to correctly classify some records as paediatric or adult and/or a lack of secondary care records (Figure 5). Estimation is possible for many more individuals in the life-limiting conditions group than in the chronic conditions group and agreement between estimation methods is greater for those with at least one secondary care record each year (i.e.

Figure 7: Density profiles for differences in age at estimated transition point between estimation methods, in pairwise comparisons



Top: whole cohort; Bottom: Frequent Care group.

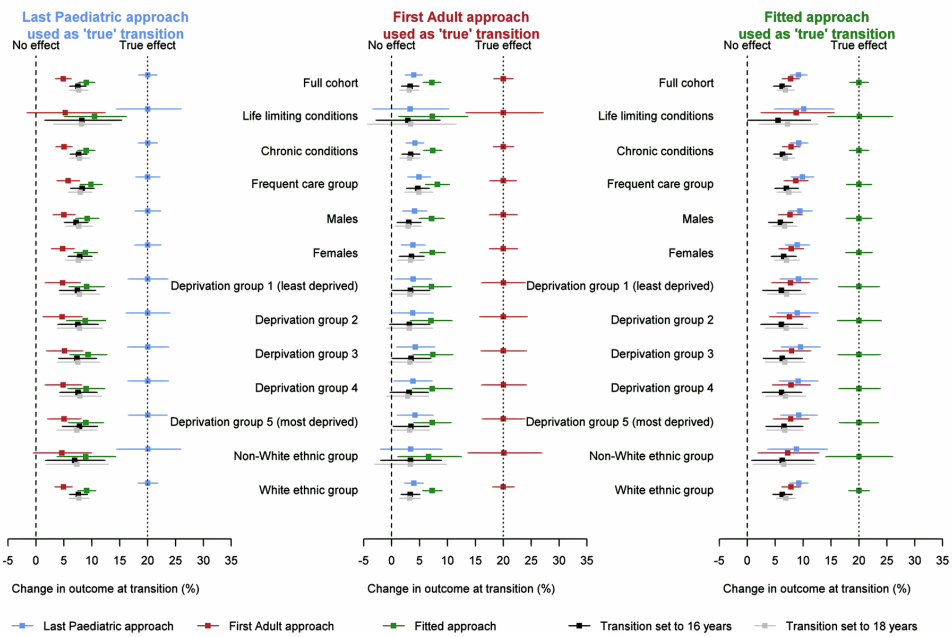
the Frequent Care group - those with more data on which to base the estimation, Figure 7).

Record classification and availability of paediatric services

There are difficulties in classification of records using treatment specialty or consultant main specialty, with many records at ages likely to be pre-transition (i.e. under 14 years) classified as adult or unclassified. This is less of a problem for children with life-limiting conditions and for inpatient records. However, inpatient records make up only a small share of the available records and using these alone would prevent or limit transition estimation for young people with no or few inpatient records.

It appears that many children receive treatment from all-age rather than specialist paediatric services. Provision of paediatric services is known to vary [49], but treatment centre information was not provided in the data, so could not be explored. Secondary care provision in the NHS in England may take place in specialist or teaching hospitals serving large communities (often large cities) and have paediatric and adult departments for many specialties or may take place in smaller District General Hospitals, which may not have as many separate adult and paediatric departments [49, 50]. It may be appropriate for a child to be treated in an all-age department in the local hospital rather than travelling further for a specialist paediatric service, depending on care needs, although there are concerns about training [50]. This has implications not only for estimating transition, but also, potentially, for care quality

Figure 8: Observed changes associated with transition, from Poisson regressions of simulated outcomes for the whole cohort and indicated subgroups



Outcome counts post-transition were drawn from a Poisson distribution with mean 20% higher than the distribution used for pre-transition outcome counts. Change in outcome as measured by the model is shown for each estimation method and for transition assumed to be always at age 16 years or age 18 years. Horizontal bars show 95% confidence intervals.

and outcomes [51–56] and may raise many of the same issues as transition itself [17, 18].

Ability to estimate transition

Transition can be estimated for the majority of young people with life-limiting conditions, particularly for those with at least one inpatient or outpatient record each year. This is important as this group is most likely to experience any impacts of transition, being in receipt of frequent health care - often from a number of providers, many of whom change at transition [17, 18]. Estimation is possible for fewer of those with chronic (but non-life-limiting) conditions, mainly due to a lack of records, but also due to a lack of classifiable records. Even among those with a record in each year from 15 to 20 years of age only a maximum of 63% (for those born in 1998) of those with a non-life-limiting chronic condition could have a transition point estimated. This may be due to treatment in all-age services, as discussed above. Chronic conditions are a broad group and some conditions will have transition estimated much more readily than others due to differences in hospital use [57, 58]. Asthma, for example, was included, but for many young people this can be managed in primary care without hospital visits [59]. There is however an upward trend in the share of those with chronic conditions for whom transition can be estimated; estimation may be possible for more of those born after 1998 as more data become available.

Comparison of estimation methods

The transition methods cannot be compared against a gold standard (as none exists for these data [20]) but only against each other and with reference to the issues outlined above.

The First Adult approach is limited by the large number of records classified as adult at ages unlikely to represent adult care (e.g. under 14 years). One strategy to compensate for this might be to add an age cut-off below which a record cannot be classified as adult. The difficulty here is in where to apply that cut-off [20]. Also, for the First Adult approach, the large number of records in childhood that are classified as adult records would mean that the age cut-off would, for many individuals, simply become the estimated age of transition and make it similar to the simpler approaches of using a universal age cut-off. The limitations in record classification mean that the First Adult approach should not be used for these data.

The Fitted Approach will also be influenced by the presence of early adult records, but to a lesser extent, due to also taking into account later paediatric records.

The Last Paediatric approach is much less affected by early adult records - they have no direct relevance, although incorrect classification of a paediatric record as adult could move the last paediatric record to a younger age.

The estimation approaches should also be considered in relation to experience of care. While it is easy to imagine a child pre-transition being occasionally treated in adult services as discussed above, it seems much less likely that an adult, formally transitioned to adult care, would receive

further treatment in a paediatric setting (although this is not completely unknown [27, 28]). There is an argument for favouring the Last Paediatric approach over the Fitted approach as it provides a transition point that is clearly defined by an experienced event (last paediatric appointment). It is at this point that access to familiar paediatric experts that the family and young person may have developed a relationship with over many years is withdrawn, so may have the most relevance to assessment of changes in healthcare use related to the changes at transition. The other approaches identify transition points at which the family and young person may still have access to the familiar paediatric services in addition to adult services. Discussions with the Martin House Research Centre Family Advisory Board suggest that this may reflect experience better than the Fitted Approach which places transition in the middle of that process. This - and its lower sensitivity to the presence young-age records classified as adult - suggests that the Last Paediatric method should be the favoured approach for these data.

Impact of estimation of transition

Use of a simple age cut-off appears likely to underestimate the association between transition status and an outcome, but the simulations do not provide evidence that it does this more for one group than another. It should be noted that some of the groups are small and this may mask differences, particularly for ethnic group where small numbers meant that only White and non-White groups were compared. There may also be systematic differences in transition age between particular conditions or by region, but there were insufficient data available in this study to explore this. Small groups with wider confidence intervals will, of course, be more likely to have confidence intervals including no effect if underestimation of effect size occurs. It is therefore possible that use of a simple age cut-off might result not only in underestimation of an association, but also in the conclusion that there is no statistically significant association at all.

There are also large differences in the simulation between the estimation methods, particularly between the Last Paediatric and First Adult approaches. The Fitted and Last Paediatric approaches do however give results more similar to each other than either compared to a simple age cut-off.

The transition estimates used as 'true' transition in the simulations will include their own errors (they will not be free of misclassification bias) and so the simulations are likely to provide an overestimate of the benefits of estimating transition. They do however highlight the importance of correctly assigning transition status.

Strengths and limitations

This study used a nationally representative sample of primary care and hospital data. Although developed using data from England, the methods are directly applicable to the other nations in the United Kingdom, with similar health services and healthcare records. The methods could be adapted to healthcare data from any country in there is a transition from paediatric to adult healthcare and in which records may be classified as paediatric or adult. Different healthcare systems, with different record information, may require different classification schemes, but the methods of estimating transition from classified records should be transferable. Different conclusions may be drawn about the most effective estimation approach in data for other countries, particularly if transition policy differs.

The Martin House Research Centre Family Advisory Board was consulted before and after analyses and helped to put the results in context and understand the real-world experience of transition and applicability of the possible methods. The estimation methods explored here arise from suggestions in the literature and discussions of healthcare transition with the Martin House Research Centre Family Advisory Board and were chosen to be meaningful with respect to young people's and families' experiences of transition.

There are also limitations, particularly in relation to the data. Splitting of main treatment specialty into paediatric and adult specialties only became widespread in England in 2007. This limits the ability to estimate transition for anyone reaching transition ages before this point as data may be incomplete. This was mitigated by excluding individuals older than 15 years in 2007, but at the expense of reducing sample size. Requirements on years present (15 to 20 years of age) also mean those who died before age 20 were excluded. Those that die before transition are not relevant to analysis of transition (as transition does not take place) but there is a significant number of young people with life-limiting conditions dying between ages 16 and 20 years, who may transition before death [60]. These (49, 4% of those with life-limiting conditions eligible for inclusion under other criteria) were excluded in this study, due to a pragmatic decision to construct a cohort for whom transition was likely to have taken place within years of available data, but there is no reason why the methods set out here could not also be applied to these individuals.

The data used also have potential issues with individuals entering and leaving the cohort due to changing GP practice from an included practice to an excluded practice. Individuals who moved practice between 15 and 20 years of age would be excluded from this study and may have different characteristics to those who remained at the same practice. Young people leaving home for work or higher education at 18 years may move GP practice and be lost from the data (possibly less of an issue for the group with life-limiting conditions for whom it may be more common to remain in the family home post-18).

Any comparison of post- and pre-transition care requires transition point to be defined, but there may not be a single well defined point of healthcare transition for all individuals [27]. As noted by the Centre's Family Advisory Board, there are a number of other disruptive transitions beyond healthcare, such as transitions in social care, education and availability of health related benefits and support [61]. This study, using healthcare data, was unable to explore any of these issues, but they should be kept in mind when studying effects of healthcare transition as alternative or additional potential causes of observed changes.

Future research

This study demonstrates the feasibility of using routinely collected healthcare data to estimate the transition point from paediatric to adult care, with potential to improve sensitivity when assessing changes in care events associated

with the transition. These methods should be applied in future research evaluating the impacts of transition, enabling use of large, nationally representative datasets with reduced risk of misclassification bias. Comparisons should also be made with use of a simple age cut-off to assess impact across a range of real-world healthcare event outcomes. Beyond the UK, the approaches outlined here should be adapted and evaluated for data from other countries that include indications of paediatric of adult care in healthcare records.

The estimation methods could also be applied to other transitions, in healthcare and beyond, for any data that include records that can be classified into two or more states. They could be used to explore transitions between health states and stages of condition, using - for example - presence or absence of particular medications.

Conclusion

The estimation of the transition point from paediatric to adult healthcare from routine healthcare data is feasible and appears to offer advantages over the use of a simple age cut-off when assessing changes in outcomes associated with transition. Among approaches explored here, using the last paediatric record to define the transition is least sensitive to known limitations of the data and may better reflect the point at which transition is experienced. These methods should be used to enable studies of transition and transition interventions in nationally representative routinely collected healthcare data with reduced risk of misclassification bias.

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Conflicts of interest

The authors have no competing interests to declare.

Ethics statement

The study was covered by general ethical approval (ref: 05/MRE04/87) for studies using Clinical Practice Research Datalink data for observational research approved by its Independent Scientific Advisory Committee (ISAC). This study was approved by ISAC (protocol ref: 19_215R).

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Abbreviations

APC:	Admitted patient care
A&E:	Accident and Emergency
CPRD:	Clinical Practice Research Datalink
GP:	General Practitioner
HES:	Hospital Episodes Statistics
ICD-10:	International Classification of Diseases 10th Revision
ISAC:	Independent Scientific Advisory Committee
NHS:	National Health Service
NIHR:	National Institute for Health Research
SQL:	Structured Query Language

Supplementary Tables: Classification system for treatment and consultant main specialties

Supplementary table 1: Classification of treatment specialties as paediatric, adult or unclassified

Treatment specialty	Paediatric	Adult	Unclassified
100 = General Surgery		Y	
101 = Urology		Y	
102 = Transplantation Surgery (Includes Renal And Liver Transplants, Excludes Cardiothoracic Transplantation)		Y	
103 = Breast Surgery (Includes Suspected Neoplasms, Cysts Etc, Does Not Include Cosmetic Surgery)		Y	
104 = Colorectal Surgery (Surgical Treatment Of Disorders Of The Lower Intestine - Colon, Anus And Rectum)		Y	
105 = Hepatobiliary & Pancreatic Surgery (Includes Liver Surgery But Excludes Liver Transplantation See Transplantation Surgery)		Y	
106 = Upper Gastrointestinal Surgery		Y	
107 = Vascular Surgery		Y	
108 = Spinal Surgery Service (From April 2013)		Y	
110 = Trauma & Orthopaedics			Y
120 = Ear, Nose And Throat (ENT)		Y	
130 = Ophthalmology		Y	
140 = Oral Surgery		Y	
141 = Restorative Dentistry (Endodontics, Periodontics And Prosthodontics)		Y	
142 = Paediatric Dentistry	Y		
143 = Orthodontics			Y
144 = Maxillo-Facial Surgery		Y	
150 = Neurosurgery		Y	
160 = Plastic Surgery		Y	
161 = Burns Care (Recognised Specialist Services Only - Includes 'Outreach' Facilities)		Y	
170 = Cardiothoracic Surgery (Where There Are No Separate Services For Cardiac And Thoracic Surgery)		Y	
171 = Paediatric Surgery	Y		
172 = Cardiac Surgery		Y	
173 = Thoracic Surgery		Y	
174 = Cardiothoracic Transplantation (Recognised Specialist Services Only - Includes 'Outreach' Facilities)		Y	
180 = Accident & Emergency (A&E)			Y
190 = Anaesthetics		Y	
191 = Pain Management (Complex Pain Disorders Requiring Diagnosis And Treatment By A Specialist Multi-Professional Team)		Y	
192 = Critical Care Medicine (Also Known As Intensive Care Medicine)		Y	
199 = Non-Uk Provider - Specialty Function Not Known, Treatment Mainly Surgical		Y	
211 = Paediatric Urology (From 2006-07)	Y		
212 = Paediatric Transplantation Surgery (From 2006-07)	Y		
213 = Paediatric Gastrointestinal Surgery (From 2006-07)	Y		
214 = Paediatric Trauma And Orthopaedics (From 2006-07)	Y		
215 = Paediatric Ear Nose And Throat (From 2006-07)	Y		
216 = Paediatric Ophthalmology (From 2006-07)	Y		
217 = Paediatric Maxillo-Facial Surgery (From 2006-07)	Y		
218 = Paediatric Neurosurgery (From 2006-07)	Y		
219 = Paediatric Plastic Surgery (From 2006-07)	Y		
220 = Paediatric Burns Care (From 2006-07)	Y		
221 = Paediatric Cardiac Surgery (From 2006-07)	Y		
222 = Paediatric Thoracic Surgery (From 2006-07)	Y		
223 = Paediatric Epilepsy (From April 2013)	Y		
241 = Paediatric Pain Management (From 2006-07)	Y		
242 = Paediatric Intensive Care (From 2006-07)	Y		

Continued

Supplementary table 1: Continued

Treatment specialty	Paediatric	Adult	Unclassified
251 = Paediatric Gastroenterology (From 2006-07)	Y		
252 = Paediatric Endocrinology (From 2006-07)	Y		
253 = Paediatric Clinical Haetology (From 2006-07)	Y		
254 = Paediatric Audiological Medicine (From 2006-07)	Y		
255 = Paediatric Clinical Immunology And Allergy (From 2006-07)	Y		
256 = Paediatric Infectious Diseases (From 2006-07)	Y		
257 = Paediatric Dermatology (From 2006-07)	Y		
258 = Paediatric Respiratory Medicine (From 2006-07)	Y		
259 = Paediatric Nephrology (From 2006-07)	Y		
260 = Paediatric Medical Oncology (From 2006-07)	Y		
261 = Paediatric Metabolic Disease (From 2006-07)	Y		
262 = Paediatric Pheumalogy (From 2006-07)	Y		
263 = Paediatric Diabetic Medicine	Y		
264 = Paediatric Cystic Fibrosis	Y		
280 = Paediatric Interventional Radiology (From 2006-07)	Y		
290 = Community Paediatrics (From 2006-07)	Y		
291 = Paediatric Neuro-Disability (From 2006-07)	Y		
300 = General Medicine		Y	
301 = Gastroenterology		Y	
302 = Endocrinology		Y	
303 = Clinical Haematology		Y	
304 = Clinical Physiology (From 2008-09)		Y	
305 = Clinical Pharmacology		Y	
306 = Hepatology		Y	
307 = Diabetic Medicine		Y	
308 = Bone And Marrow Transplantation (Previously Part Of Clinical Haematology)		Y	
309 = Haemophilia (Previously Part Of Clinical Haematology)		Y	
310 = Audiological Medicine		Y	
311 = Clinical Genetics		Y	
313 = Clinical Immunology And Allergy		Y	
314 = Rehabilitation Service		Y	
315 = Palliative Medicine		Y	
316 = Clinical Immunology		Y	
317 = Allergy Service		Y	
318 = Intermediate Care		Y	
319 = Respite Care		Y	
320 = Cardiology		Y	
321 = Paediatric Cardiology	Y		
322 = Clinical Microbiology		Y	
323 = Spinal Injuries (From 2006-07)		Y	
324 = Anticoagulant Service		Y	
325 = Sport And Exercise Medicine		Y	
327 = Cardiac Rehabilitation		Y	
328 = Stroke Medicine		Y	
329 = Transient Ischaemic Attack		Y	
330 = Dermatology		Y	
331 = Congenital Heart Disease Service (From April 2013)		Y	
340 = Respiratory Medicine (Previously Known As Thoracic Medicine)		Y	
341 = Respiratory Physiology (Previously Known As Sleep Studies)		Y	
342 = Programmed Pulmonary Rehabilitation		Y	
343 = Adult Cystic Fibrosis Service		Y	
344 = Complex Specialised Rehabilitation Service (From April 2013)		Y	
345 = Specialist Rehabilitation Service (From April 2013)		Y	
346 = Local Specialist Rehabilitation Service (From April 2013)		Y	
350 = Infectious Diseases		Y	
352 = Tropical Medicine		Y	

Continued

Supplementary table 1: Continued

Treatment specialty	Paediatric	Adult	Unclassified
360 = Genitourinary Medicine		Y	
361 = Nephrology		Y	
370 = Medical Oncology		Y	
371 = Nuclear Medicine (From 2008-09)		Y	
400 = Neurology		Y	
401 = Clinical Neurophysiology (From 2008-09)		Y	
410 = Rheumatology		Y	
420 = Paediatrics	Y		
421 = Paediatric Neurology	Y		
422 = Neonatology		Y	
424 = Well Babies (Care Given By The Mother/Substitute, With Nursing AdviceNeeded)		Y	
430 = Geriatric Medicine		Y	
450 = Dental Medicine Specialities		Y	
460 = Medical Ophthalmology		Y	
501 = Obstetrics		Y	
502 = Gynaecology		Y	
503 = Gynaecological Oncology		Y	
560 = Midwifery Service		Y	
650 = Physiotherapy (From 2006-07)			Y
651 = Occupational Therapy (From 2006-07)		Y	
652 = Speech And Language Therapy (From 2006-07)		Y	
653 = Podiatry (From 2006-07)		Y	
654 = Dietetics (From 2006-07)			Y
655 = Orthoptics (From 2006-07)		Y	
656 = Clinical Psychology (From 2006-07)			Y
657 = Prosthetics		Y	
658 = Orthotics		Y	
659 = Drama Therapy		Y	
660 = Art Therapy		Y	
661 = Music Therapy		Y	
662 = Optometry		Y	
663 = Podiatric Surgery (From April 2013)		Y	
700 = Learning Disability (Previously Known As Mental Handicap)		Y	
710 = Adult Mental Illness		Y	
711 = Child And Adolescent Psychiatry	Y		
712 = Forensic Psychiatry		Y	
713 = Psychotherapy		Y	
715 = Old Age Psychiatry		Y	
720 = Eating Disorders (From 2006-07)		Y	
721 = Addiction Services (From 2006-07)		Y	
722 = Liaison Psychiatry (From 2006-07)		Y	
723 = Psychiatric Intensive Care(From 2006-07)		Y	
724 = Perinatal Psychiatry (From 2006-07)		Y	
725 = Mental Health Recovery And Rehabilitation Service (From April 2013)		Y	
726 = Mental Health Dual Diagnosis Service (From April 2013)		Y	
727 = Dementia Assessment Service (From April 2013)		Y	
800 = Clinical Oncology (Previously Known As Radiotherapy)		Y	
811 = Interventional Radiology		Y	
812 = Diagnostic Imaging (From 2008-09)			Y
822 = Chemical Pathology		Y	
834 = Medical Virology		Y	
840 = Audiology (From 2008-09)		Y	
920 = Diabetic Education Service (From April 2013)			Y

Supplementary table 2: Classification of consultant main specialties as paediatric, adult or unclassified

Consultant main specialty	Paediatric	Adult	Unclassified
100 = General Surgery		Y	
101 = Urology		Y	
110 = Trauma And Orthopaedics		Y	
120 = Ear, Nose And Throat (Ent)		Y	
130 = Ophthalmology		Y	
140 = Oral Surgery		Y	
141 = Restorative Dentistry		Y	
142 = Paediatric Dentistry (Available From 1999-2000)		Y	
143 = Orthodontics		Y	
145 = Oral And Maxillo Facial Surgery (Available From 2004-05)		Y	
146 = Endodontics (Available From 2004-05)		Y	
147 = Periodontics		Y	
148 = Prosthodontics (Available From 2004-05)		Y	
149 = Surgical Dentistry (Available From 2004-05)		Y	
150 = Neurosurgery		Y	
160 = Plastic Surgery		Y	
170 = Cardiothoracic Surgery		Y	
171 = Paediatric Surgery	Y		
180 = Accident And Emergency (A&E)			Y
190 = Anaesthetics		Y	
191 = Pain Management (Available From 1998-99 To 2003-04)		Y	
192 = Critical Care Medicine (Available From 2004-05)		Y	
300 = General Medicine		Y	
301 = Gastroenterology		Y	
302 = Endocrinology		Y	
303 = Clinical Haematology		Y	
304 = Clinical Physiology		Y	
305 = Clinical Pharmacology		Y	
310 = Audiological Medicine		Y	
311 = Clinical Genetics		Y	
312 = Clinical Cytogenics And Molecular Genetics (Available From 1990-91)		Y	
313 = Clinical Immunology And Allergy (Available From 1991-92)		Y	
314 = Rehabilitation (Available From 1991-92)		Y	
315 = Palliative Medicine		Y	
320 = Cardiology		Y	
321 = Paediatric Cardiology (Available From 2004-05)	Y		
325 = Sport And Exercise Medicine		Y	
326 = Acute Internal Medicine		Y	
330 = Dermatology		Y	
340 = Respiratory Medicine (Also Known As Thoracic Medicine)		Y	
350 = Infectious Diseases		Y	
352 = Tropical Medicine (Available From 2004-05)		Y	
360 = Genito-Urinary Medicine		Y	
361 = Nephrology		Y	
370 = Medical Oncology		Y	
371 = Nuclear Medicine		Y	
400 = Neurology		Y	
401 = Clinical Neuro-Physiology		Y	
410 = Rheumatology		Y	
420 = Paediatrics	Y		
421 = Paediatric Neurology	Y		
430 = Geriatric Medicine		Y	
450 = Dental Medicine (Available From 1990-91)		Y	
451 = Special Care Dentistry		Y	
460 = Medical Ophthalmology (Available From 1993-94)		Y	
499 = Non-Uk Provider - Specialty Function Not Known, Treatment Mainly Medical		Y	

Continued

Supplementary table 2: Continued

Consultant main specialty	Paediatric	Adult	Unclassified
500 = Obstetrics And Gynaecology		Y	
501 = Obstetrics (Prior To 2004-05: Obstetrics For Patients Using A Hospital Bed Or Delivery Facilities)		Y	
502 = Gynaecology		Y	
504 = Community Sexual And Reproductive Health		Y	
560 = Midwifery (Available From October 1995)		Y	
600 = General Medical Practice		Y	
601 = General Dental Practice		Y	
610 = General Practice With Maternity Function (Available To 2003-04)		Y	
620 = General Practice Other Than Maternity (Available To 2003-04)		Y	
700 = Learning Disability (Previously Known As Mental Handicap)		Y	
710 = Adult Mental Illness		Y	
711 = Child And Adolescent Psychiatry			Y
712 = Forensic Psychiatry		Y	
713 = Psychotherapy		Y	
715 = Old Age Psychiatry (Available From 1990-91)		Y	
800 = Clinical Oncology (Previously Radiotherapy)		Y	
810 = Radiology		Y	
820 = General Pathology		Y	
821 = Blood Transfusion		Y	
822 = Chemical Pathology		Y	
823 = Haematology		Y	
824 = Histopathology		Y	
830 = Immunopathology		Y	
831 = Medical Microbiology And Virology		Y	
832 = Neuropathology (Available To 2003-04)		Y	
833 = Medical Microbiolody		Y	
834 = Medical Virology		Y	
900 = Community Medicine		Y	
901 = Occupational Medicine		Y	
902 = Community Health Services - Dental (Available From 2004-05)		Y	
903 = Public Health Medicine (Available From 2004-05)		Y	
904 = Public Health Dental (Available From 2004-05)		Y	
950 = Nursing Episode (Available From 2002-03)		Y	
960 = Allied Health Professional Episode (Available From 2006-07)		Y	

A1.4 Paper 4: Adult healthcare is associated with more emergency healthcare for young people with life-limiting conditions

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The published paper is reproduced in the following pages.

The supplementary materials are provided in Appendix 2, beginning on page 212, including:

Please see Section 9.49.1 for discussion of other relevant issues identified since publication of this paper.

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POPULATION STUDY ARTICLE OPEN

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Adult healthcare is associated with more emergency healthcare for young people with life-limiting conditions

Stuart Jarvis[1]✉, Kate Flemming[2], Gerry Richardson[3] and Lorna Fraser[1]

BACKGROUND: Children with life-limiting conditions receive specialist paediatric care in childhood, but the transition to adult care during adolescence. There are concerns about transition, including a lack of continuity in care and that it may lead to increases in emergency hospital visits.

METHODS: A retrospective cohort was constructed from routinely collected primary and hospital care records for young people aged 12–23 years in England with (i) life-limiting conditions, (ii) diabetes or (iii) no long-term conditions. Transition point was estimated from the data and emergency inpatient admissions and Emergency Department visits per person-year compared for paediatric and adult care using random intercept Poisson regressions.

RESULTS: Young people with life-limiting conditions had 29% (95% CI: 14–46%) more emergency inpatient admissions and 24% (95% CI: 12–38%) more Emergency Department visits in adult care than in paediatric care. There were no significant differences associated with the transition for young people in the diabetes or no long-term conditions groups.

CONCLUSIONS: The transition from paediatric to adult healthcare is associated with an increase in emergency hospital visits for young people with life-limiting conditions, but not for young people with diabetes or no long-term conditions. There may be scope to improve the transition for young people with life-limiting conditions.

Pediatric Research; https://doi.org/10.1038/s41390-022-01975-3

IMPACT:

- There is evidence for increases in emergency hospital visits when young people with life-limiting conditions transition to adult healthcare.
- These changes are not observed for comparator groups - young people with diabetes and young people with no known long-term conditions, suggesting they are not due to other transitions happening at similar ages.
- Greater sensitivity to changes at transition is achieved through estimation of the transition point from the data, reducing misclassification bias.

INTRODUCTION

There are many young people with life-limiting conditions—conditions that either shorten life, such as Duchenne Muscular Dystrophy, or conditions that threaten to shorten life, but may be cured, such as cancer[1] —with ~86,000 in the United Kingdom and at least 500,000 in the United States.[2,3]

In childhood, care is normally led by a paediatric specialist. In the late teenage years, care transitions to adult services.[4,5] Adult services are often coordinated in primary rather than secondary or tertiary care, but these providers can lack expertise and training in life-limiting conditions, despite efforts at improvement.[6] Transition can seem abrupt,[5,7] varying between health conditions and with availability and remit of local services.[5,8,9] There is often no equivalent adult service.[10] There can be a lack of follow-up, gaps in care and a lack of standardised transition.[11–13]

Any increase in emergency care at transition has implications for health service costs and may cause emotional trauma for young people and their families.[14–19] Existing evidence on healthcare use at transition shows mixed findings,[20] mainly from small, unrepresentative studies or larger studies with a simple age-based classification of transition.[21] Transition age can vary widely,[5,8,9] so these studies risk misclassification bias, with potential underestimation of transition effects.[22–24]

Transition can be managed well; research on transition for diabetes has suggested improved transition pathways.[25–36] Diabetes, therefore, makes a good comparison group to life-limiting conditions to understand what changes might be expected under a well-established transition process. There are also other transitions at similar ages, such as changes in education and employment and increases in risk-taking behaviours that could affect emergency hospital use. Young people with no long-term health care conditions—and, therefore, no meaningful healthcare transition—are therefore another relevant comparison group.

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This study aims to establish whether there is an increase in emergency inpatient admissions and Emergency Department visits when children with life-limiting conditions transition to adult healthcare using a nationally representative dataset.

METHODS

Patient and public involvement

The Martin House Research Centre Family Advisory Board was consulted (the Board is one key part of the Centre's PPI strategy[37] and comprises parents and carers who either have or had children with life-limiting conditions). Transition experiences of families of children with life-limiting illness influenced the choice of comparator groups and informed the development of methods for estimating transition point and the final choice of approach.[22] Their insights aided interpretation, as set out in the Discussion.

Datasets

Nationally representative linked primary and secondary healthcare data from the Clinical Practice Research Datalink (CPRD, data from a sample of primary care providers in England) were used. CPRD identified all individuals in the CPRD 'GOLD' dataset aged 12–23 years at any point from 1 January 2000 to 31 December 2018. All records, while aged 0–23 years, were requested along with linked, Hospital Episode Statistics Admitted Patient Care (2000–2018), Outpatient (2000–2018) and Emergency Department (2007–2018) datasets. The datasets were linked by CPRD using National Health Service number, sex, date of birth and postcode.[38]

The study falls under ethical approval (ref: 05/MRE04/87) for observational research CPRD data approved by its Independent Scientific Advisory Committee (ISAC). ISAC approval was gained (protocol ref: 19_215R).

Data management

Population of interest. Three groups of young people were of interest, as set out above: (i) those with life-limiting conditions, (ii) those with diabetes, and (iii) those with no known long-term conditions. Group membership depended on diagnoses in primary care, inpatient and outpatient records while aged 12–23 years:

1. Young people were assigned to the life-limiting conditions group if any diagnosis in the HES records matched a previously developed International Classification of Diseases, 10th Edition[39] (ICD-10) coding framework[40] or if any diagnosis in primary care records matched a Read coding framework[41] derived from the ICD-10 coding framework.
2. Young people were assigned to the diabetes group, if not in the life-limiting conditions group and if any diagnosis in the HES or primary care records matched ICD-10 or Read codes for diabetes, derived from a previously developed list of chronic conditions diagnoses[42] (see also Supplementary Material S1).
3. Young people were assigned to the no long-term conditions group if not in the other groups and if they had no matches in HES or primary care records against previously developed coding frameworks that identified health conditions likely (i.e. in more than 50% of cases) to require follow-up (hospital admissions, outpatient visits, medications) for more than 1 year.[42,43]

Young people not assigned to a group—i.e. those with a chronic condition other than diabetes or one of the life-limiting conditions—were excluded (Fig. 1).

Identification of transition point. Transition points from paediatric to adult healthcare were estimated from the data for the life-limiting condition and diabetes groups, using a previously developed method.[22] Transition point was identified by first classifying inpatient and outpatient records from age 14 years onwards for young people in the life-limiting conditions or diabetes groups as paediatric or adult based on treatment and consultant main speciality codes (Supplementary Material S2) and then applying rules to define transition point from these records (Fig. 2). Transition prior to 14 years was considered unrealistic, so records before 14 years were not considered.[5,6]

For young people in the life-limiting condition or diabetes groups, year of transition from children's to adult care was set as the year containing the last paediatric record, as long as there was an adult record after the last recorded paediatric record.[22] Those who died or left the dataset before age 23 years without an adult record after the last paediatric record were considered not to have undergone transition and were excluded from analysis (Figs. 1 and 2). Those who reached age 23 years without an adult record after the last paediatric record, due to a lack of secondary care records, were assigned transition at age 16. A sensitivity analysis set transition for all young people with no transition point estimated from the data to age 16 years (Supplementary Material S3).

For the no long-term condition group, transition year was set as 16 years after the year of birth (i.e. age 16 years).

Years before the estimated year of transition were considered paediatric healthcare. The year of transition and later years were considered adult healthcare.

An a priori decision was made to require presence for the last two years of paediatric care and the first two years of adult care (sensitivity analyses explored variations—see Supplementary Material S3). This meant anyone in the no long-term conditions group born after 2001 was excluded (as they were no older than 16 years at the study end in 2018 and so did not have two years of adult data). For consistency between groups, all young people born after 2001 were excluded.

Young people born before 1992 were excluded as they were unlikely to have records classified as paediatric (most paediatric specialities were introduced in 2007—anyone born before 1992 was already aged 16 years by 2007).

Cohort identification. A retrospective cohort was constructed (Fig. 1) including all young people who satisfied all the following criteria:

1. Were in the life-limiting conditions, diabetes or no long-term conditions groups.
2. Were born no earlier than 1992 and no later than 2001.
3. Had a transition point estimated.
4. Were present in the CPRD data for at least two years of paediatric care and two years of adult care.

Demographic data. Sex, year of birth, and deprivation category (derived from the 2015 Index of Multiple Deprivation based on last known address) were provided in CPRD data. Ethnic group was provided by CPRD as the group most commonly recorded in the linked HES data.

Analyses

Description of cohort. Numbers of individuals in the cohort were summarised by condition group and demographics.

Transition age. Estimated age at transition was summarised for the life-limiting condition and diabetes groups

Emergency hospital visits. Numbers of emergency inpatient admissions and Emergency Department visits per person-year were summarised by age, condition group, sex and transition status (paediatric or adult care). Confidence intervals were estimated by bootstrapping (10,000 replications).

Statistical models. The two primary outcomes, number of inpatient admissions and Emergency Department visits were assessed in separate regression models.

Associations of numbers of emergency inpatient admissions with transition status: The outcomes were count data with repeated observations (one each year) clustered within individuals; a two-level (level 1: individual, level 2: year) random intercept Poisson regression was used.[44] Over-dispersion, at least due to un-modelled differences between individuals, was accounted for by the random intercept.[44] The independent variable of interest, transition status, was binary (1: adult; 0: paediatric). Other candidate variables were:

- Condition group (level 1) as healthcare use was expected to differ across these groups.
- Age (level 2) as healthcare use varies with age.[41,45]
- Sex (level 1) as healthcare use varies by sex.[41,45]
- Ethnic group (level 1) as healthcare use varies by ethnic group.[41]
- Deprivation category (level 1) as healthcare use varies by deprivation.[41,46]

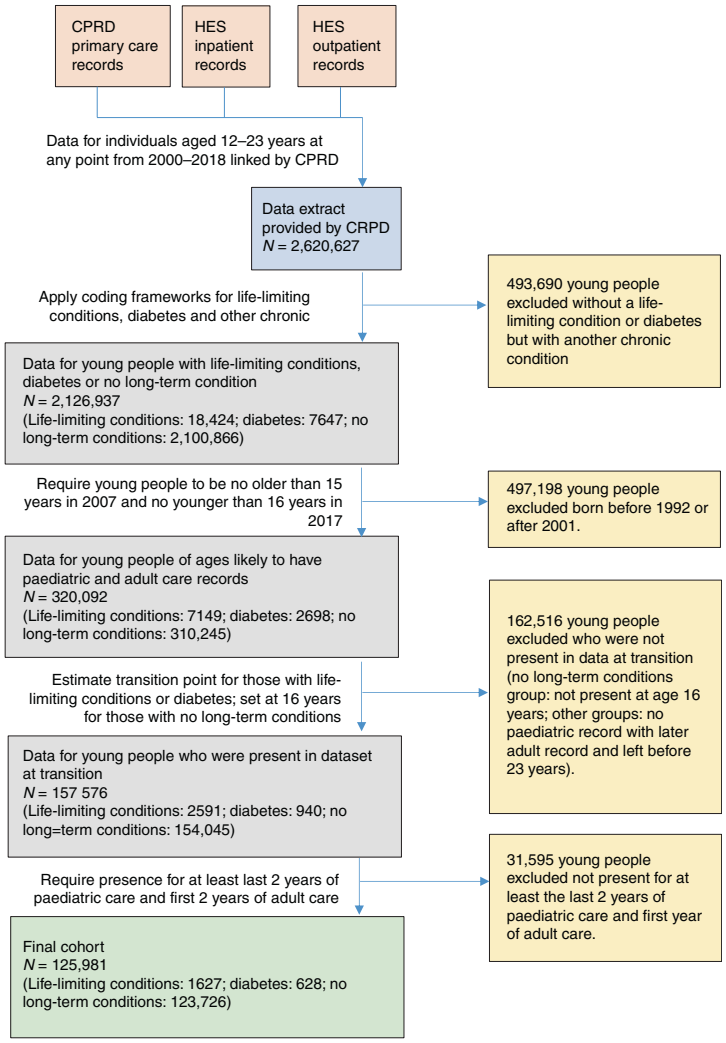

Fig. 1 Cohort construction. Datasets held by CPRD are shown in pink; the final dataset provided to the authors by CPRD if shown in blue; grey boxes indicate processing steps; yellow boxes indicate exclusions and green boxes indicate the final data used in analyses. Arrows show data flows.

- Year of birth (level 1) reflecting cohort effects if care practices changed over time.

Interactions were also considered:

- Between age and sex and condition group, as healthcare use varies with age in different ways for males and females[45] and may differ by condition group.
- Between transition status and condition group (it was expected that condition group would modify associations between transition and emergency hospital visits).

Reduction of the Bayesian Information Criterion by more than 3 was grounds for retention of variables and interactions.[47]

Time at risk (when present in the CPRD data and not a hospital inpatient) was included.

Associations of numbers of Emergency Department visits with transition status: A random intercept Poisson regression was used. Methods were the same as for emergency inpatient admissions, with the same candidate covariates and interactions.

Population-level estimates. Estimates were made of changes in emergency inpatient admissions and Emergency Department visits associated with the transition for all young people with life-limiting conditions in England (Fig. 3). Numbers of young people aged 14–17 and 18–23 years with life-limiting conditions in England were estimated from 2017 (the most recently available) figures from a previously published full-population study.[48] The proportion of young people aged 14–17 and 18–23 years in the present study data who were in the first two years of adult healthcare was calculated using estimated transition points, to give the number of young people aged 14–17 and 18–23 years in England in the first two years of adult healthcare (matching the period analysed in this study). Regression models from the present study were used to calculate expected numbers of emergency inpatient admissions and Emergency Department visits for members of the study cohort aged 14–17 and

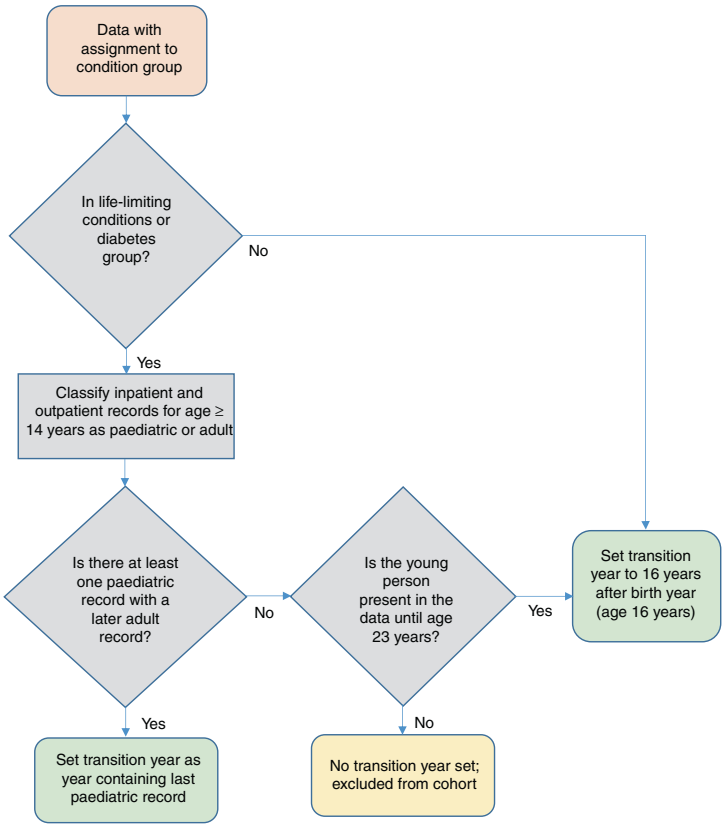

Fig. 2 Flow chart of estimation of the transition point from the data. Pink box shows source data for the process; grey boxes show decisions and intermediate processing steps; green boxes show final outcomes for included data and yellow boxes show final outcomes for excluded data.

18–23 years within this group if (a) they had remained in paediatric healthcare and (b) had transitioned to adult healthcare. These estimates for events per person per year were then multiplied by the number of young people nationally aged 14–17 and 18–23 years and in the first two years of adult care. The difference between these estimates was the expected difference in emergency hospital visits associated with the transition at the population level.

Confidence intervals in the final estimates were based on confidence intervals for the estimates from the regression models as the uncertainty from these models dominated other uncertainties.

RESULTS

Cohort summary

There were 125,981 individuals in the final cohort (Fig. 1). There were more males than females in all three groups (Fig. 1 and Table 1). Comparisons between ethnic groups were hampered by large numbers of missing data in the no long-term conditions group (>50%). Less deprived groups were over-represented in the cohort as a whole (Table 1) but the distribution in the life-limiting conditions group was more even, with ~20% in each of the five deprivation categories.

Transition age

The most common transition age for diabetes and life-limiting conditions was 18 years, but the distribution was more closely grouped around 18 years for diabetes (Fig. 4). 1% of those with life-limiting conditions had transition assigned to age 16 years due to a lack of paediatric and adult records; all in the diabetes group had transition estimated from the data.

Emergency hospital visits

Emergency inpatient admissions. The life-limiting conditions and diabetes groups had the highest rates of emergency admissions, at 0.28 (95% CI 0.26–0.31) and 0.26 (95% CI: 0.23–0.29) per person-year, respectively, (Table 2) and did not differ significantly (difference 0.02, 95% CI: −0.01–0.06). The no long-term conditions group had a lower rate, 0.0162 (95% CI: 0.0160–0.0164) per person-year.

Females had more emergency inpatient admissions than males in the life-limiting conditions and diabetes groups (Table 2 and Fig. 5), by 0.07 (95% CI: 0.01–0.12) in the life-limiting conditions group and 0.13 (95% CI: 0.07–0.18) in the diabetes group per person year. For no long-term conditions, males had 0.0040 (95% CI: 0.0031–0.0035) more admissions per person-year than females. Trends by age differed between sexes (Fig. 5) with increases with age for both males and females in the life-limiting conditions group (although mostly within 95% confidence intervals); decreases for males with diabetes up to age 19 years and no clear change for females; and increases for females and decreases for males in the no long-term conditions group.

In the life-limiting conditions group, those in adult care had 0.06 (95% CI: 0.03–0.09) more emergency admissions per person-year than those in paediatric care (Table 2 and Fig. 6). There were no

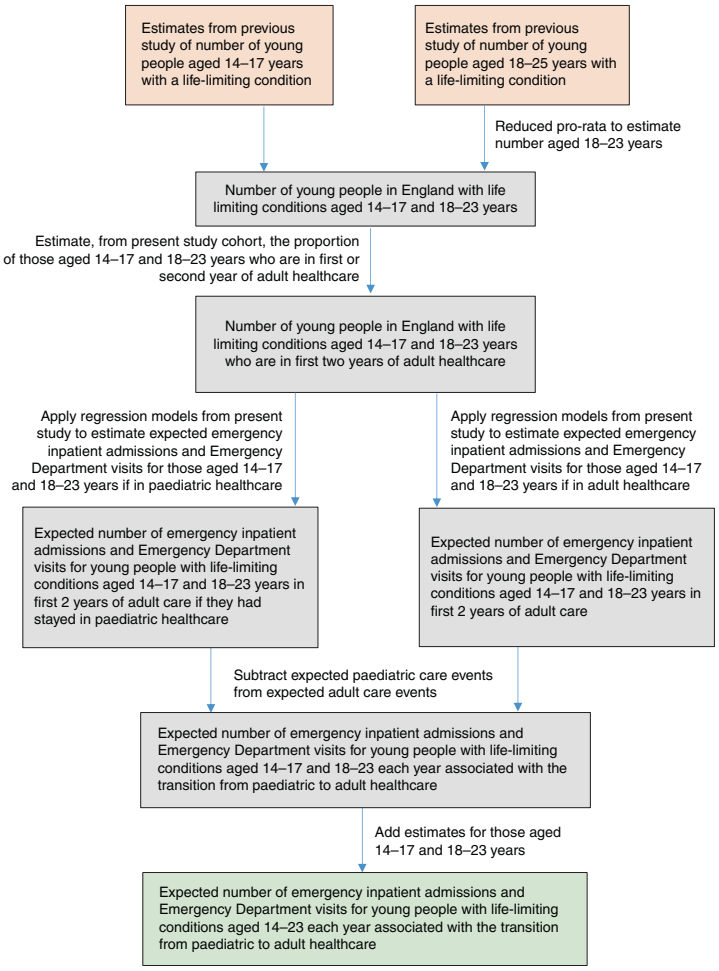

Fig. 3 Construction of population-level estimates. Estimates of numbers additional emergency inpatient admissions and Emergency Department visits associated with a transition from paediatric to adult healthcare were combined with national estimates of young people aged 14–23 years with life-limiting conditions.

significant differences for the other groups. Differences varied by age in the life-limiting conditions group (Fig. 6), with those aged 16 years in adult care having fewer emergency admissions than those in paediatric care at the same age; at most other ages point estimates were higher in adult care than paediatric care.

Emergency Department visits. The life-limiting conditions and diabetes groups had the highest rates of Emergency Department visits, at 0.55 (95% CI: 0.51–0.58) and 0.65 (95% CI: 0.59–0.70) per person-year respectively (Table 2); visits were higher in the diabetes group (by 0.10, 95% CI: 0.03–0.16). The no long-term conditions group had fewer visits: 0.197 (95% CI: 0.196–0.198) per person-year.

Females with life-limiting conditions and diabetes had more visits per person-year than males (Table 2 and Fig. 5) by, respectively, 0.11 (95% CI: 0.03–0.19) and 0.11 (95% CI: 0.01–0.22). Males with no long-term conditions (Table 2) had 0.069 (95% CI: 0.066–0.071) more visits than females. Trends by age differed between sexes (Fig. 5) with greater increases with increasing age for females than for males.

In the life-limiting conditions group, those in adult care had 0.13 (95% CI: 0.08–0.18) more visits per person-year than those in paediatric care (Table 2 and Fig. 6). There were no significant differences for the diabetes group. In the no long-term conditions group, those in adult care had 0.006 (95% CI: 0.004–0.008) more visits than those in paediatric care. Differences varied by age in the life-limiting conditions group (Fig. 6), with those aged 16–17 years in adult care having little difference in point estimates for visits compared to those in paediatric care at the same age, although at most other ages point estimates were higher for the group in adult care. There were no clear differences by transition status for the diabetes group. For the no long-term conditions group, those in adult care had more visits than those in paediatric care, but were also older.

Statistical models

The final regression models included transition status (adult or paediatric care), age in year, sex, ethnic group, deprivation category,

Table 1. Cohort characteristics.

	Life-limiting conditions group	Diabetes group	No long-term conditions group	Full cohort
All in group	1627	628	123,726	125,981
Sex				
Males	920[a] (56%)	350[a] (56%)	66,020[a] (53%)	67,290[a] (53%)
Females	710[a] (44%)	280[a] (44%)	57,710[a] (47%)	58,690[a] (47%)
Unknown	≤10 (≤1%)	≤10 (≤1%)	≤10 (≤1%)	≤10 (≤1%)
Ethnic group				
Bangladeshi	≤10 (≤1%)	≤10 (≤2%)	153 (<1%)	162 (<1%)
Black	54 (3%)	≤10 (1%)	1334 (1%)	1396 (1%)
Indian	16 (1%)	≤10 (1%)	629 (1%)	649 (1%)
Pakistani	32 (2%)	≤10 (≤2%)	573 (<1%)	615 (1%)
White	1400 (86%)	573 (2%)	50,444 (41%)	52,417 (42%)
Mixed and other	64 (4%)	189 (91%)	2553 (<1%)	2635 (2%)
Unknown	50[a] (3%)	10[a] (≤2%)	68,040 (54%)	68,107 (54%)
Deprivation category				
1 (least deprived)	340[a] (21%)	150[a] (23%)	34,158 (28%)	34,644 (27%)
2	320[a] (19%)	130[a] (21%)	25,738 (21%)	26,183 (21%)
3	320[a] (19%)	110[a] (18%)	24,107 (19%)	24,532 (19%)
4	320[a] (20%)	140[a] (22%)	20,651 (17%)	21,106 (17%)
5 (most deprived)	340[a] (21%)	110[a] (17%)	18,983 (15%)	19,426 (15%)
Unknown	≤10 (≤1%)	≤10 (≤2%)	90[a] (<1%)	90 (<1%)

Demographics are described for each of the condition groups and for the whole cohort.
Percentages are within the condition group.
[a]Indicates numbers rounded to the nearest 10 to prevent disclosure of censored numbers (≤10) in other cells.

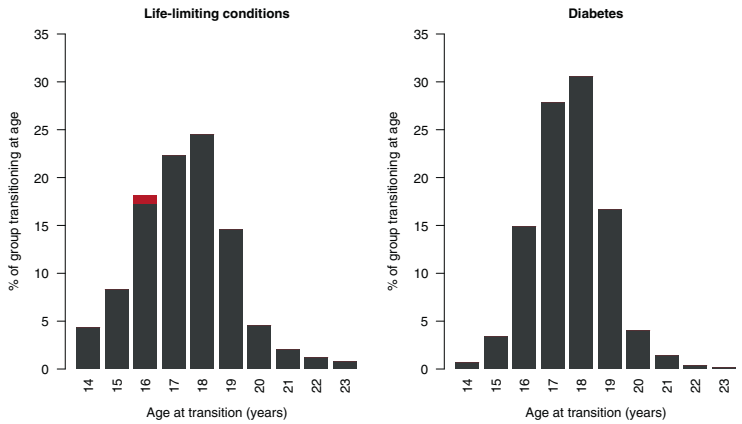

Fig. 4 Distribution of transition ages in the life-limiting conditions and diabetes groups. Red sections on the bar for age 16 years indicates group members assigned this transition age due to lacking both a paediatric and an adult record (there were no such members in the diabetes group).

condition group, an interaction between transition status and condition group and an interaction between condition group, age and sex (Table 3). Sensitivity analyses excluding deprivation category and ethnic group and including the year of birth are presented in Supplementary Material S3.

Emergency inpatient admissions. Young people in adult care in the life-limiting conditions group had 29% (95% CI: 14–46%) more emergency inpatient admissions than those in paediatric care. There were no significant differences associated with the transition for the other groups (Table 4).

Emergency Department visits. Young people in the life-limiting conditions group in adult care had 24% (95% CI: 12–38%) more Emergency Department visits than those in paediatric care. There were no significant differences associated with the transition for the other groups (Table 4). A gradient was observed with deprivation for Emergency Department visits, with the most

Table 2. Emergency hospital visits by conditions group, sex and transition status.

Group	Emergency inpatient admissions per 100 person years (95% CI)			Emergency Department visits per 100 person years (95% CI)		
	Life-limiting conditions	Diabetes	No long-term conditions	Life-limiting conditions	Diabetes	No long-term conditions
All	28 (25–31)	26 (23–29)	1.62 (1.60–1.64)	55 (51–58)	65 (59–70)	19.7 (19.6–19.8)
Males	25 (22–28)	21 (18–23)	1.78 (1.76–1.81)	50 (46–53)	60 (52–66)	22.9 (22.7–23.0)
Females	32 (27–37)	33 (28–38)	1.43 (1.40–1.46)	61 (54–68)	71 (64–79)	16.0 (15.8–16.1)
Paediatric care	27 (24–30)	27 (24–30)	16.2 (1.60–1.65)	51 (48–55)	64 (59–69)	19.6 (19.5–19.7)
Adult care	33 (29–37)	24 (20–28)	1.61 (1.55–1.67)	65 (58–71)	67 (57–76)	20.2 (20.0–20.5)

For ease of comparison of rare events (emergency inpatient admissions for those with no long-term conditions) these are expressed by 100 person years.

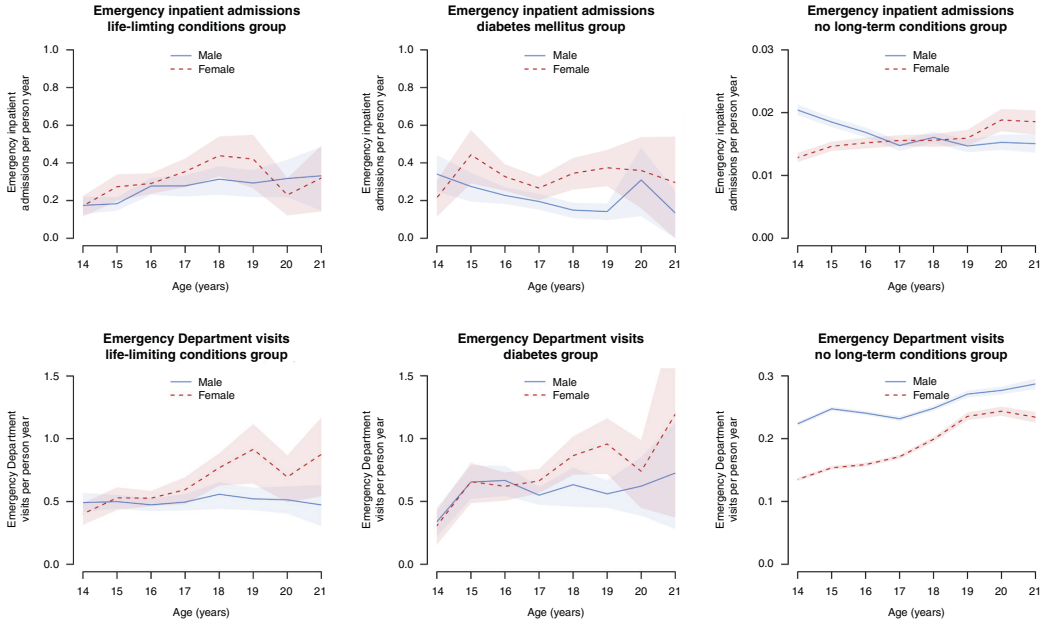

Fig. 5 Numbers of emergency healthcare events by age and sex. Numbers of emergency inpatient admissions and Emergency Department visits recorded per person-year in the cohort, split by age and sex, with 95% confidence intervals (shaded areas) estimated by bootstrapping.

deprived groups having 31% (95% CI: 27–35%) more visits than the least deprived group.

Population-level estimates

For young people with life-limiting conditions aged 14–23 years and in their first two years of adult care, the regression models predict an extra 753 (95% CI: 550–1031) emergency inpatient admissions and an extra 1201 (95% CI: 876–1630) Emergency Department visits each year compared to remaining in paediatric care (see also Supplementary Material S4 for splits by 14–17 and 18–23 years age groups).

DISCUSSION

This study showed an increase in unplanned hospital visits associated with the transition from paediatric to adult healthcare for young people with life-limiting conditions, of 29% (95% CI: 14–46%) for emergency inpatient admissions and 24% (95% CI: 12–38%) for Emergency Department visits. No significant change in unplanned hospital visits was found for the diabetes and no long-term conditions groups.

The changes associated with the transition for the life-limiting conditions group are equivalent to an extra 753 (95% CI: 550–1031) emergency inpatient admissions and 1201 (95% CI: 876–1630) Emergency Department visits each year.

Variations by condition group

Findings for the condition groups differed greatly, with associations found between transition and unplanned hospital visits for the life-limiting conditions groups, but not for the diabetes and no long-term conditions groups.

For the no long-term conditions group, there should be no meaningful healthcare transition —hospital visits should be mainly ad-hoc and so it would be usual to see a different healthcare practitioner in a different department for each visit. There is no additional discontinuity in care around age 16 years—consistent with the observed lack of an association between transition status and emergency hospital visits.

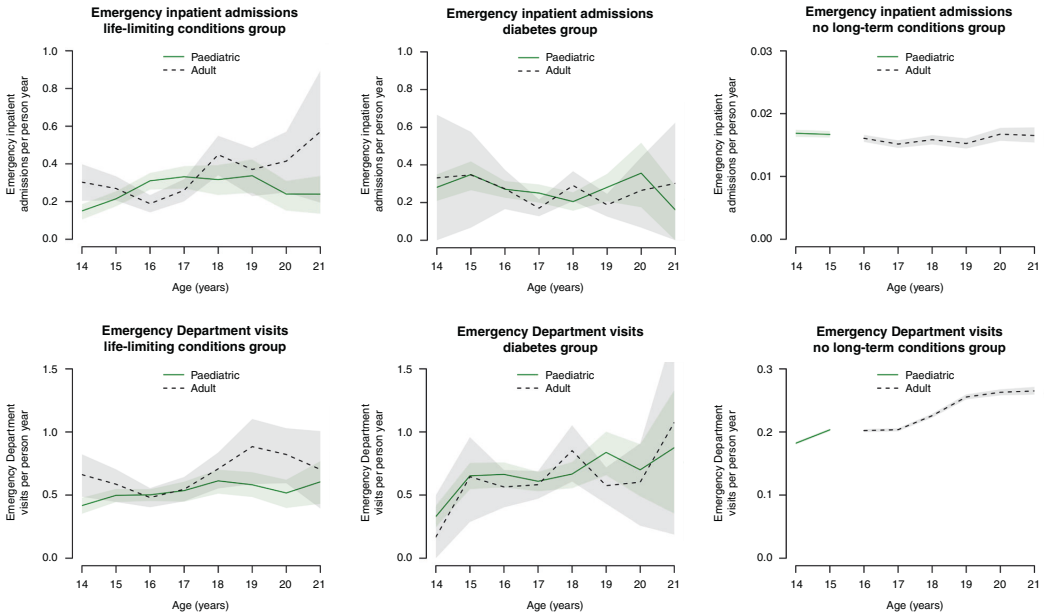

Fig. 6 Numbers of emergency healthcare events by age and transition status. Numbers of emergency inpatient admissions and Emergency Department visits recorded per person-year in the cohort, split by age and transition status, with 95% confidence intervals (shaded areas) estimated by bootstrapping.

No change at transition was found for the diabetes group. A previous review for diabetes found mixed evidence on hospital use around transition, from increases to no change.[35] Established transition pathways may minimise impact.[25,26,30,33,34] Young people with diabetes are a far more homogenous group than young people with life-limiting conditions, with similar treatments and complications. Many primary care practitioners would have the ongoing experience of caring for young people with diabetes. They have fewer complex needs and less need for associated services, such as physiotherapy, that transition could disrupt. Transition ages were more tightly clustered for the diabetes group than for the life-limiting conditions group, which may reflect greater uniformity in processes or needs. The present study shows that transition from paediatric to adult services does not necessarily have to lead to an increase in emergency hospital visits. There may be scope to reduce unplanned hospital visits after transition for the life-limiting conditions group by learning lessons from the transition processes for diabetes, particularly around greater care continuity being associated with reduced risk of hospitalisation.[31,33] For diabetes, unlike for some life-limiting conditions, there are adult services closely equivalent to paediatric services. Continuity and knowledge in primary care have been cited as helpful by members of the Martin House Research Centre Family Advisory Board and in previous studies.[41,49]

For young people with life-limiting conditions, the findings are consistent with some previous studies that found evidence of increases in inpatient admissions at transition.[20,50–53] Studies finding fewer inpatient admissions post-transition were clustered in Canada[54–57] and looked at all admissions, not only emergency inpatient admissions. They also, unlike the present study, did not estimate transition point from the data. One study looking at emergency inpatient admissions found conflicting evidence for males and females, but across a narrow range of blood conditions.[58] The findings of increased Emergency Department visits associated with the transition are consistent with the majority of previous studies looking at this outcome.[20,55,56,59,60] The findings were consistent with the experiences of the Martin House Research Centre Family Advisory Board, who cited a switch to more reactive rather than preventive care after transition, poorer condition management, inconsistency in staff seen in primary care and subsequent lack of understanding and trust as possible reasons for increases in emergency hospital visits, factors backed up by other studies.[7,13,31,41]

Implications of findings

The models demonstrate associations, not causality, but the comparator groups of diabetes and no long-term conditions exclude some other possible explanations such as inevitable changes in healthcare-seeking behaviours around transition ages or changes related to risk-taking behaviours. Increases in unplanned hospital visits associated with the transition will have emotional and financial impacts on young people with life-limiting conditions and their families.[14–19,61] Emergency inpatient admissions, at least, may also be indicative of a deteriorating or poorly managed condition, with longer-term implications for ongoing care needs and quality of life. The population-level estimates put the observed changes at transition in perspective. They look only at the first two years of adult care (sensitivity analyses suggest that associations persist for longer) so represent a conservative estimate.

There is a clear contrast between the life-limiting conditions and diabetes groups in the present study. Both groups of young people undergo a meaningful transition from paediatric to adult healthcare, with changes in care providers and an expectation for the young person to play a greater role in condition management.[5–13,25–36] However, in the present study, increases in emergency healthcare use are only observed for the life-limiting conditions group. Transition for young people with diabetes is not free of problems,[35] but there is generally a defined transition process[62] and adult services have broadly similar provision to child

Table 3. Regression models for emergency healthcare events.

	Emergency inpatient admissions				Accident and Emergency Department visits			
	Incidence rate ratio	95% confidence interval		*P* value	Incidence rate ratio	95% confidence interval		*P* value
Age (per year of age)	0.90	0.88	0.93	<0.01	1.02	1.01	1.03	<0.01
Sex								
Male	1 (ref)				1 (ref)			
Female	0.06	0.03	0.12	<0.01	0.23	0.18	0.28	<0.01
Ethnic group								
Bangladeshi	1.32	0.86	2.02	0.20	0.81	0.60	1.08	0.15
Black African	1.52	1.12	2.05	0.01	1.00	0.83	1.21	0.98
Black Caribbean	1.07	0.69	1.64	0.77	0.94	0.79	1.12	0.49
Black Other	0.88	0.65	1.20	0.41	0.92	0.80	1.05	0.21
Chinese	1.07	0.69	1.67	0.76	0.58	0.45	0.74	<0.01
Indian	0.77	0.60	0.99	0.04	0.64	0.57	0.72	<0.01
Mixed	1.07	0.88	1.30	0.48	1.11	0.99	1.25	0.08
Other Asian	1.02	0.78	1.34	0.88	0.77	0.67	0.89	<0.01
Other	0.86	0.72	1.03	0.11	0.88	0.80	0.96	0.01
Pakistani	0.77	0.58	1.02	0.07	0.79	0.70	0.90	<0.01
White	1 (ref)				1 (ref)			
Unknown	0.03	0.03	0.04	<0.01	0.48	0.47	0.49	<0.01
Deprivation category								
1 (least deprived)	1 (ref)				1 (ref)			
2	0.92	0.85	0.99	0.03	1.03	1.00	1.06	0.02
3	0.95	0.88	1.02	0.17	1.11	1.08	1.14	<0.01
4	1.06	0.98	1.14	0.14	1.21	1.18	1.25	<0.01
5 (most deprived)	1.06	0.97	1.15	0.19	1.31	1.27	1.35	<0.01
Condition group								
No long-term condition	1 (ref)				1 (ref)			
Diabetes	6.63	0.96	45.61	0.06	2.16	0.57	8.27	0.26
Life-limiting condition	1.62	0.50	5.26	0.42	2.36	1.09	5.11	0.03
Transition status								
Paediatric care	1 (ref)				1 (ref)			
Adult care	1.00	0.94	1.06	1.00	1.01	0.99	1.02	0.46
Sex × age interaction[a]								
Female (per year of age)	1.18	1.13	1.24	<0.01	1.07	1.06	1.09	<0.01
Condition group × age interaction[a]								
Diabetes (per year of age)	1.00	0.89	1.13	0.95	0.99	0.91	1.06	0.71
Life-limiting conditions (per year of age)	1.10	1.03	1.18	0.01	0.97	0.92	1.02	0.26
Condition group × sex × age interaction[a]								
Diabetes and female (per year of age)	0.99	0.83	1.18	0.91	1.11	0.99	1.25	0.08
Life-limiting conditions and female (per year of age)	0.85	0.76	0.95	0.01	1.03	0.96	1.11	0.34
Condition group × transition status interaction[a]								
Diabetes and adult care	0.83	0.67	1.01	0.07	0.93	0.82	1.06	0.30
Life-limiting condition and adult care	1.29	1.13	1.48	<0.01	1.24	1.12	1.37	<0.01

Regression model incidence rate ratio for two-level Poisson regressions on the numbers of emergency inpatient admissions and number of Emergency Department visits per cohort member per year.
[a]Indicates there are omitted combinations of interactions (reference groups with an incident rate ratio 1).

services, albeit with often less frequent contact, and diabetes is commonly managed in primary care.[63] While there are concerns about discontinuity, young people with diabetes are also focused on the challenges of taking greater responsibility for their care and the interaction with other behavioural changes and life events at similar ages—changes in education and in risk-taking behaviours.[35] This is in contrast to services for young people with life-limiting conditions where there may not be an equivalent adult

Table 4. Differences in emergency healthcare use between adult and paediatric care.

Group	Emergency inpatient admissions				Accident and Emergency Department visits			
	Incidence rate ratio (adult compared to paediatric care)	95% confidence interval		P value	Incidence rate ratio (adult compared to paediatric care)	95% confidence interval		P value
Life-limiting conditions	1.29	1.14	1.46	<0.01	1.24	1.12	1.38	<0.01
Diabetes	0.83	0.68	1.00	0.06	0.94	0.83	1.07	0.35
No long-term conditions	1.00	0.94	1.06	1.00	1.01	0.99	1.02	0.46

Combined incidence rate ratios (taking account of interactions) for emergency inpatient admissions and Emergency Department visits.

service,[10] there may be little expertise in particular conditions among primary can practitioners[6] and transition processes can vary by condition.[5,8,9]

The results for diabetes show that the transition from children's to adult healthcare does not necessarily have to be associated with an increase in emergency hospital care. However, it does not follow that simply copying the diabetes transition would improve care for young people with life-limiting conditions. The latter group have more diverse healthcare needs which may be less easily met by primary care generalists and are likely to require at least partly condition-specific transition programmes.

Strengths and limitations

This study has a number of strengths. Unlike many previous studies, it uses nationally representative routinely collected healthcare data, so reduces the risk of bias from—for example—small groups within a single clinic. It also estimates the transition point from the data, increasing sensitivity to detect changes in healthcare use associated with the transition.[22] It makes use of comparison groups, suggesting observed changes are not due to non-healthcare transitions occurring at similar ages. Sensitivity analyses were used to test impacts key assumptions and analysis decisions, particularly around years of data to include in the regressions.

There are also limitations. There may be power issues for the relatively small diabetes group. The study sample size was chosen based on simulations of a 20% change in outcomes at transition, so while any changes at transition for the diabetes group can be expected to be less than 20%, smaller changes may be present that this study was not powered to detect. There were many missing data for ethnic group, but mostly for the no long-term conditions group, with more than 50% missing. Sensitivity analyses suggest this had little effect on estimates. There will also likely be some individuals for whom transition point was misidentified or for whom transition was a multi-year process. These issues are however likely to be fewer and smaller than in other studies that used a simple age cut-off to assign transition status. Finally, healthcare transitions are not the only transitions taking place during the years of data included in the study. Other transitions, particularly in education or employment can also happen at similar ages and impacts may differ between condition groups. As noted by the Martin House Research Centre Family Advisory Board, young people with life-limiting conditions may have attended specialist schools with regular access to nurses, so school transitions may be more impactful on health outcomes for this group than for the others.

Future research

The findings of this study suggest that there is an increase in emergency hospital visits in the first two years of adult healthcare. Further studies are needed to understand this, looking—through qualitative research—at the experiences of young people with life-limiting conditions as they transition.

There is also a need for research into other aspects of healthcare at transition, including other measures of secondary care use (e.g. length of stay, bed days per year) and measures of primary care use, such as GP contacts. The relationships, if any, between primary and secondary care use before and after transition should also be explored. Costs, to both healthcare providers and young people and their families, should also be assessed to help understand the scope for cost-effective changes in care.

Understanding experiences and needs, as well as a full picture of healthcare use, across the transition, will help to focus future research on possible areas of intervention. Any interventions should be rigorously assessed for impact.

CONCLUSION

The transition from paediatric to adult healthcare is associated with an increase in emergency hospital visits for young people with life-limiting conditions. Such an increase is not seen for young people with diabetes or no long-term conditions.

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AUTHOR CONTRIBUTIONS

S.J. conceptualised and designed the study, obtained the data, conducted the analyses, and reviewed and revised the manuscript, and gave final approval of the version to be published. K.F. contributed to the design of the study, reviewed the analyses and reviewed and revised the manuscript, and gave final approval of the version to be published. G.R. contributed to the design of the study, reviewed the analyses and reviewed and revised the manuscript, and gave final approval of the version to be published. L.F. helped conceptualise the study, contributed to the design of the study, reviewed the analyses, and reviewed and revised the manuscript, and gave final approval of the version to be published.

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COMPETING INTERESTS

The authors declare no competing interests.

CONSENT STATEMENT

Patient consent was not required for this study.

ADDITIONAL INFORMATION

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A1.5 Paper 5: GPs' role in caring for children and young people with life-limiting conditions: a retrospective cohort study (Objective 5)

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The published paper is reproduced in the following pages.

The supplementary materials are provided in Appendix 2, beginning on page 280, including:

Please see Section 9.5 for discussion of other relevant issues identified since publication of this paper.

Stuart Jarvis, Roger C Parslow, Catherine Hewitt, Sarah Mitchell and Lorna K Fraser

GPs' role in caring for children and young people with life-limiting conditions:

a retrospective cohort study

Abstract

Background
GPs are rarely actively involved in healthcare provision for children and young people (CYP) with life-limiting conditions (LLCs). This raises problems when these children develop minor illness or require management of other chronic diseases.

Aim
To investigate the association between GP attendance patterns and hospital urgent and emergency care use.

Design and setting
Retrospective cohort study using a primary care data source (Clinical Practice Research Datalink) in England. The cohort numbered 19 888.

Method
CYP aged 0–25 years with an LLC were identified using Read codes (primary care) or *International Classification of Diseases 10th Revision* (ICD-10) codes (secondary care). Emergency inpatient admissions and accident and emergency (A&E) attendances were separately analysed using multivariable, two-level random intercept negative binomial models with key variables of consistency and regularity of GP attendances.

Results
Face-to-face GP surgery consultations reduced, from a mean of 7.12 per person year in 2000 to 4.43 in 2015. Those consulting the GP less regularly had 15% (95% confidence interval [CI] = 10% to 20%) more emergency admissions and 5% more A&E visits (95% CI = 1% to 10%) than those with more regular consultations. CYP who had greater consistency of GP seen had 10% (95% CI = 6% to 14%) fewer A&E attendances but no significant difference in emergency inpatient admissions than those with lower consistency.

Conclusion
There is an association between GP attendance patterns and use of urgent secondary care for CYP with LLCs, with less regular GP attendance associated with higher urgent secondary healthcare use. This is an important area for further investigation and warrants the attention of policymakers and GPs, as the number of CYP with LLCs living in the community rises.

Keywords
child; continuity of care; emergency healthcare use; general practice; life-limiting condition; primary health care.

INTRODUCTION

There are more than 40 000 children and young people (CYP) living with a life-limiting condition (LLC) in England.[1,2] Almost 400 diagnoses are considered as life limiting in children.[3] These include conditions for which there is no reasonable hope of cure and from which the CYP will die, and conditions for which curative treatment may be feasible but can fail, such as cancer or heart failure. Severe static neurodisability, such as cerebral palsy and severe congenital anomalies, are also included.

CYP with an LLC typically have complex healthcare needs, and during childhood tertiary or community paediatricians provide their care. The role of GPs in their care is an area that requires further consideration, particularly for children with cancer.[4] Regional analyses in the West Midlands estimated that the numbers of CYP with an LLC may be almost double the number of GPs.[5] However, GPs are rarely actively involved in the provision of health care to CYP with LLCs. This raises particular problems when these CYP develop minor childhood illness, require primary care review, or have other chronic conditions, such as asthma, that require regular medication.[6] Furthermore, many of these CYP are transferred back to the GP to coordinate their care when they become too old for paediatric services.[7]

There is evidence, from the US, of high numbers of hospital admissions for this population,[8,9] and a lack of confidence among general physicians in caring for them;[10] however, there is no UK-based research that has quantified the role of the GP in the care of CYP with LLCs. Increasing GP understanding of these conditions and involvement in the care of CYP with complex needs is being referred to in national strategy and guidance documents,[11,12] and by the organisations that campaign for and support these families.[13]

This study aimed to assess the association between face-to-face GP surgery consultations and emergency healthcare use in CYP with an LLC in a nationally representative data source.

Patient and public Involvement

Parents of CYP with an LLC identified this topic area[14] as they felt that their GP lacked sufficient knowledge of their child's condition, and, therefore, always contacted the hospital or went to A&E rather than their GP. They also described difficulties with the transition process to adult services, mainly around lack of coordination of care.

METHOD

Participants

Datasets. All Clinical Practice Research Datalink (CPRD)[15] Gold primary care (2000–

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How this fits in

Children with life-limiting conditions (LLCs) are high users of health care. GPs have a key role in the management of patients with LLCs and complexity, including children. However, children's health care is often specialist led and GPs are less involved. Primary care studies in adult populations demonstrate the value of continuity of care. This has been compromised by changes in the organisation of GP services, including out-of-hours provision and GP contracting. This study suggests that the consistent and regular involvement of a GP in the care of children with an LLC is associated with reduced emergency secondary care use. This is the first study of its type to examine the potential impact of regular GP attendance and continuity of care with a GP for paediatric patients with LLCs.

2015), Hospital Episodes Statistics Admitted Patient Care (HES APC) (2000–2015), and accident and emergency (A&E, 1 April 2007 to 31 March 2015) records were requested from CPRD for individuals matching the cohort definition (see Supplementary Figure S1). The datasets were linked by CPRD using NHS number, sex, date of birth, and postcode.[15] Denominator population data were provided by CPRD.

Cohort identification. A Read code framework was developed using similar methods to a previously developed *International Classification of Diseases 10th Revision* (ICD-10)[16] coding framework[2] for identifying LLCs. A retrospective cohort was constructed including all CYP (aged 0–25 years) with an LLC recorded in either their primary care record (Read code) or hospital episodes admitted patient care dataset (HES; ICD-10 codes; 2000–2015).

Data management. Sex and year of birth (and month of birth if <16 years old) were provided in CPRD data. Deprivation category (split into five groups using the Index of Multiple Deprivation 2010, based on the last known address of the individual[17]) was provided as linked data. Ethnic group (11 categories: black African, black Caribbean, black other, Chinese, Bangladeshi, Indian, Pakistani, other Asian, white, mixed, or other)[18] was recorded in the linked HES data; where an individual had more than one ethnic group provided, it was set by CPRD to the most commonly recorded value, excluding unknown.[15]

The LLC diagnoses were assigned into 11 diagnostic groups: circulatory, congenital, gastrointestinal, genitourinary, haematology, metabolic, neurology, oncology, perinatal, respiratory, and other. The commonest diagnostic group in the individual's records was assigned as the main diagnostic group. If there was a tie then older records were progressively ignored until there was a most common diagnostic group.

Statistical analysis

Data analyses were performed using Stata version 15.

GP attendance. The number of GP attendances (face-to-face surgery consultations) per person were calculated by year, sex, ethnic group, age group, main diagnostic group, and deprivation category. These were compared with previously published levels in the general population,[19] and confidence intervals (CIs) for the cohort figures were determined by bootstrapping with 10 000 samples.

Consistency of GP seen. Consistency of GP seen was determined for each CYP each year by calculating the usual provider of care (UPC) index (the proportion of a patient's face-to-face surgery consultations with the most regularly seen GP).[20] A minimum of two GP attendances in 1 year were required for this value to be calculated.

Regularity of GP attendance. Regularity of GP attendance was determined for each cohort member each year by calculating the mean and standard deviation of the gap between GP attendances (including

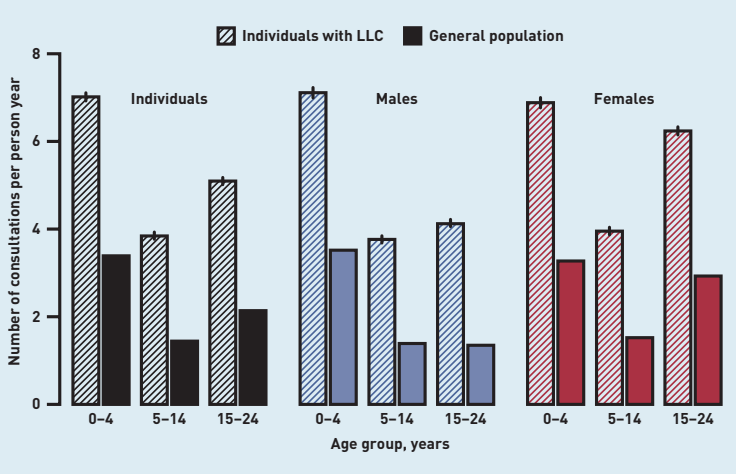

Figure 1. Face-to-face GP consultations per cohort member per year compared with those for the general population in financial year 2013/2014.[a]
[a]Vertical lines are bootstrapped 95% confidence intervals for the cohort. LLC = life-limiting condition.

attendances in the year and the gap from the last attendance of the previous year, if there was one, to the first attendance of the year under consideration). The coefficient of variation (the standard deviation of consultation gaps divided by the mean of consultation gaps[21]) was used to describe regularity. A minimum of two gaps between GP attendances (including the gap from last attendance of the previous year) were required for this value to be calculated.

Outcome measures. The number of emergency inpatient admissions and A&E attendances was calculated per individual by year, sex, ethnic group, age group, main diagnostic group, and deprivation category, and was compared with levels in the general population.[22,23] CIs for the cohort figures were determined by bootstrapping with 10 000 samples.

Multivariable models. Four multivariable models were undertaken, two for each outcome measure (emergency inpatient admissions and A&E attendances). All used a two-level random intercept (to account for clustering at individual patient level) negative binomial model because of overdispersion of these data.[24]

The independent variable of interest in the first pair of models was UPC index at level 1 (per person per year). This was split into three categories with: less than half of appointments with the most commonly seen GP (that is, there was no 'normally seen' GP), half or more but less than two-thirds of appointments with the most commonly seen GP, and two-thirds or more of appointments with the most commonly seen GP. The other variables were: at level 1, age group; at level 2 (per person), sex, ethnic group, deprivation category, and main diagnostic group. The variables included have been shown to predict levels of unplanned care for children with complex conditions.[25] Time at risk was included in the model. In the second pair of models, the independent variable of interest was coefficient of variation at level 1 (per person per year). This was split into four categories with approximately equal numbers of cohort members in each. The other variables were the same as for the first pair of models.

RESULTS

There were 19 888 individuals identified with an LLC in this cohort, rising per year from 2293 in 2000 to a high of 9055 in 2013 (see Supplementary Table S1). There were more males (53.7%, *n* = 10 666) than females (46.3%, *n* = 9222) and the predominant ethnic group was white (81.6%). The commonest main diagnostic groups were congenital (33.6%, *n* = 6741) and oncology (20.2%, *n* = 4051). More cohort members lived in areas of highest deprivation (20.7%, *n* = 4222) than in areas of lowest deprivation (18.9%, *n* = 3774).

Missing data

There were no missing data for sex, month, and year of birth. Nineteen individuals had unknown deprivation category (<1%) and 845 had unknown ethnic group (4.2%).

GP attendance

The number of face-to-face GP surgery consultations per person year reduced over the study period, from a mean of 7.12 per person year in 2000 to 4.43 in 2015 (see Supplementary Table S1). Those <1 year old had the most consultations per year; rates decreased through early years of age to a low at 11 years of age before increasing (see Supplementary Figure S2). CYP with an LLC had more GP attendances than members of the general population in the same age groups in 2013/2014 (Figure 1).

Consistency of GP seen. Mean UPC index increased from age 1 year to age 10 years, before plateauing between 0.52 and 0.55 (Figure 2a). Between 29% and 44% of cohort members in each year did not have a UPC index calculated because of having <2 consultations in the year.

Regularity of GP attendance. Children aged <1 year had the greatest regularity of face-to-face consultations (mean coefficient of variation 0.82; median 0.81, Figure 2b). Between 37% and 46% of cohort members in each year did not have a coefficient of variation calculated because of having <2 gaps between consultations in the year.

Emergency inpatient admission

The mean number of emergency inpatient admissions per person year decreased over the study period, from 0.94 in 2000 to 0.55 in 2015 (see Supplementary Table S1). Cohort members had more emergency inpatient admissions than the general population, across all groups from age 0–25 years (Figure 3a).

Multivariable models. The UPC index was not significantly associated with incidence of emergency inpatient admission (Table 1). Children aged <1 year had the most emergency admissions: 3.52 (95% CI = 3.33 to 3.72) times as many as 1–5-year-olds. Emergency admissions decreased with

Table 1. Associations between consistency of GP seen and emergency inpatient admissions and A&E attendances for the cohort: multilevel random intercept negative binomial regression models for years 2000–2015 (inpatient admissions) and 2008–2015 (A&E attendances)[a]

	Emergency inpatient admission				A&E visit			
	Incidence rate ratio	95% CI		*P*-value	Incidence rate ratio	95% CI		*P*-value
Usual provider of care index								
<1/2	1 (ref)				1 (ref)			
≥1/2, <2/3	1.01	0.98	1.05	0.40	0.95	0.91	0.98	<0.01
≥2/3	1.03	0.99	1.07	0.18	0.90	0.86	0.94	<0.01
Undefined (<2 consultations in year)	1.02	0.98	1.06	0.35	0.80	0.76	0.83	<0.01
No. of consultations in year	1.04	1.03	1.04	<0.01	1.03	1.03	1.03	<0.01
Year	0.96	0.95	0.96	<0.01	1.03	1.03	1.04	<0.01
Sex								
Male	1 (ref)				1 (ref)			
Female	1.03	0.99	1.07	0.20	0.94	0.91	0.98	0.01
Ethnic group								
Black African	1.12	0.96	1.31	0.15	1.06	0.92	1.22	0.45
Black Caribbean	1.30	1.04	1.63	0.02	1.50	1.19	1.89	<0.01
Black other	1.38	1.07	1.77	0.01	1.49	1.19	1.88	<0.01
Bangladeshi	1.16	0.84	1.60	0.38	0.91	0.68	1.23	0.56
Chinese	0.83	0.56	1.23	0.37	1.05	0.72	1.54	0.80
Indian	0.86	0.73	1.01	0.07	0.93	0.79	1.08	0.34
Pakistani	1.07	0.94	1.22	0.31	0.99	0.87	1.12	0.88
Other Asian	1.35	1.13	1.61	<0.01	1.24	1.05	1.46	0.01
White	1 (ref)				1 (ref)			
Mixed	1.24	1.08	1.42	<0.01	1.16	1.02	1.32	0.02
Other	1.09	0.93	1.27	0.30	1.19	1.03	1.38	0.02
Age group, years								
<1	3.52	3.33	3.72	<0.01	1.94	1.78	2.10	<0.01
1–5	1 (ref)				1 (ref)			
6–10	0.47	0.45	0.49	<0.01	0.66	0.63	0.69	<0.01
11–15	0.45	0.42	0.47	<0.01	0.70	0.66	0.74	<0.01
16–20	0.44	0.42	0.46	<0.01	0.73	0.69	0.77	<0.01
21–25	0.44	0.41	0.46	<0.01	0.81	0.76	0.85	<0.01
Main diagnostic group								
Circulatory	1.79	1.56	2.06	<0.01	1.22	1.06	1.39	0.01
Congenital	1 (ref)				1 (ref)			
Gastrointestinal	2.82	2.38	3.35	<0.01	1.32	1.12	1.55	<0.01
Genitourinary	3.07	2.79	3.38	<0.01	1.65	1.50	1.82	<0.01
Haematology	1.85	1.68	2.04	<0.01	1.19	1.08	1.31	<0.01
Metabolic	1.99	1.79	2.21	<0.01	1.34	1.20	1.49	<0.01
Neurology	1.71	1.60	1.82	<0.01	1.33	1.25	1.41	<0.01
Oncology	1.95	1.83	2.08	<0.01	1.02	0.96	1.08	0.58
Perinatal	0.88	0.75	1.04	0.14	0.96	0.83	1.12	0.64
Respiratory	2.29	2.12	2.46	<0.01	1.28	1.19	1.38	<0.01
Other	1.53	1.23	1.90	<0.01	1.22	1.00	1.49	0.05
Deprivation category								
1 (least deprived)	0.72	0.67	0.77	<0.01	0.63	0.59	0.67	<0.01
2	0.75	0.70	0.80	<0.01	0.66	0.62	0.71	<0.01
3	0.82	0.77	0.88	<0.01	0.78	0.73	0.83	<0.01
4	0.95	0.89	1.01	0.10	0.86	0.80	0.91	<0.01
5 (most deprived)	1 (ref)				1 (ref)			
Model parameters								
Degrees of freedom	38				38			
Log likelihood	−91 308.9				−63 513.0			
BIC	183 056.2				127 447.1			

[a] *'No. of consultations in year' and 'Year' are continuous variables — incident rate ratios indicate the expected proportional change in outcome rate for one additional consultation and 1 year later in time. A&E = accident and emergency. BIC = Bayesian information criterion.*

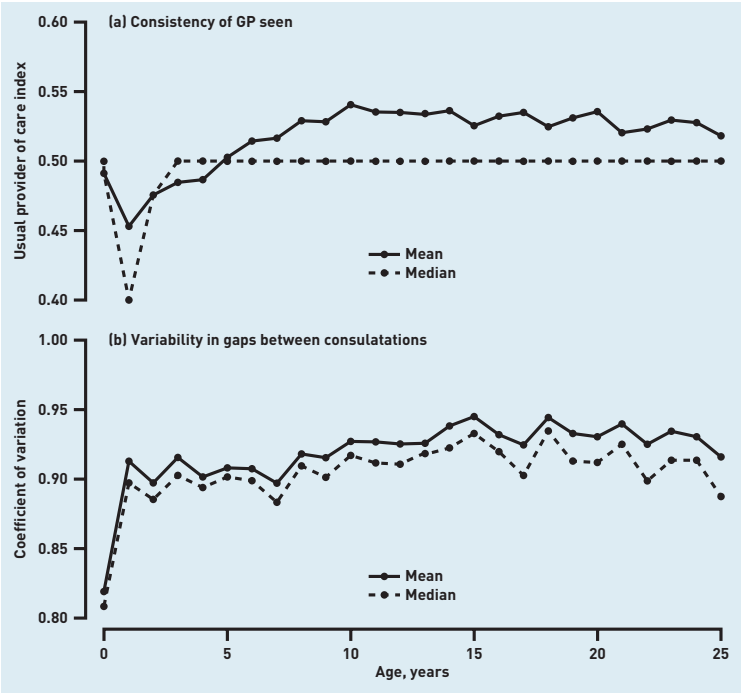

Figure 2. (a) Consistency of GP seen (usual provider of care index) for cohort members with ≥2 face-to-face GP consultations in a year and (b) variability of gaps between GP consultations (coefficient of variation) for cohort members with ≥2 gaps between consultations defined in a year.

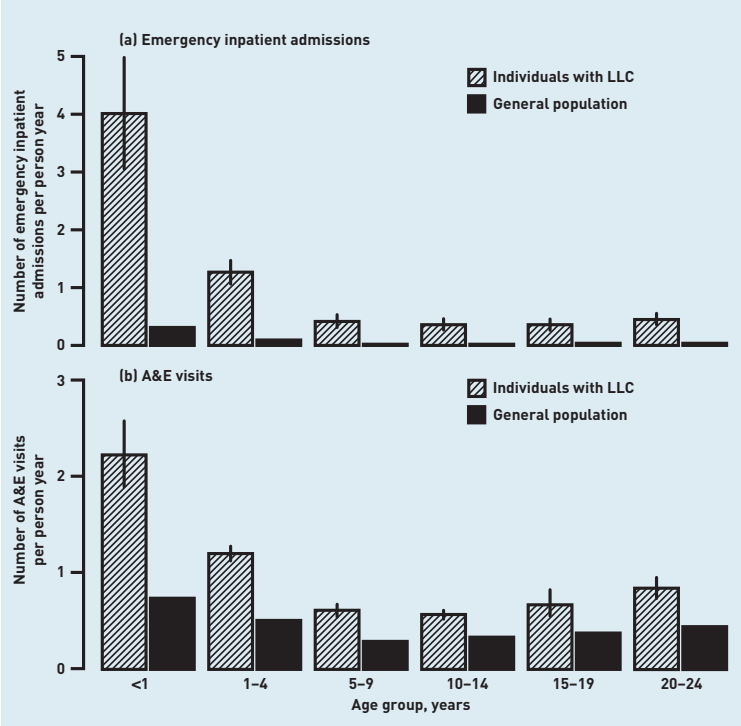

Figure 3. Emergency care use for cohort members compared with the general population by age group. (a) Emergency inpatient admissions in 2015; (b) A&E visits in 2013–2015. Vertical lines are bootstrapped 95% confidence intervals for the cohort.
A&E = accident and emergency. LLC = life-limiting condition.

increasing age. Incidence of emergency admissions differed by main diagnostic group, with those with a genitourinary diagnosis having most: 3.07 (95% CI = 2.79 to 3.38) times as many as those with a congenital main diagnosis. There was a gradient by deprivation category, with the least deprived having 28% (95% CI = 23% to 33%) fewer emergency admissions than the most deprived.

Less regular GP consultations were associated with more emergency admissions, with those having most variation having 15% (95% CI = 10% to 20%) more emergency admissions than those with least variation (Table 2).

Those children with too few GP consultations to be assigned a coefficient of variation also had significantly more emergency admissions (by 24%; 95% CI = 19% to 29%). The other variables were similar to the previous model.

A&E attendances

A&E attendances per person year increased over the study period, from 0.60 in 2008 to 0.76 in 2015 (see Supplementary Table S1). Cohort members had more A&E attendances than the general population, across all age groups (Figure 3b).

Table 2. Associations between regularity of GP appointments and emergency inpatient admissions and A&E attendances for the cohort: multilevel random intercept negative binomial regression models for all years 2000–2015 (inpatient admissions) and 2008–2015 (A&E attendances)[a]

	Emergency inpatient admission				A&E visit			
	Incidence rate ratio	95% CI		*P*-value	Incidence rate ratio	95% CI		*P*-value
Coefficient of variation for gaps between consultations								
<0.75	1 (ref)				1 (ref)			
≥0.75, <0.95	1.05	1.01	1.09	0.01	1.01	0.97	1.05	0.63
≥0.95, <1.20	1.07	1.03	1.12	<0.01	1.04	0.99	1.08	0.10
≥1.20	1.15	1.10	1.20	<0.01	1.05	1.01	1.10	0.03
Undefined (<2 consultation gaps in year)	1.24	1.19	1.29	<0.01	0.91	0.88	0.95	<0.01
No. of consultations in year	1.04	1.04	1.04	<0.01	1.03	1.03	1.03	<0.01
Year	0.96	0.95	0.96	<0.01	1.03	1.03	1.04	<0.01
Sex								
Male	1 (ref)				1 (ref)			
Female	1.04	1.00	1.08	0.08	0.95	0.91	0.99	0.02
Ethnic group								
Black African	1.11	0.95	1.30	0.17	1.06	0.92	1.22	0.43
Black Caribbean	1.31	1.04	1.64	0.02	1.49	1.19	1.88	<0.01
Black other	1.39	1.09	1.79	0.01	1.50	1.19	1.89	<0.01
Bangladeshi	1.16	0.84	1.61	0.37	0.92	0.68	1.24	0.58
Chinese	0.83	0.56	1.23	0.35	1.06	0.72	1.55	0.78
Indian	0.86	0.73	1.01	0.07	0.93	0.79	1.08	0.34
Pakistani	1.07	0.94	1.22	0.30	0.99	0.87	1.13	0.89
Other Asian	1.36	1.14	1.61	<0.01	1.24	1.06	1.46	0.01
White	1 (ref)				1 (ref)			
Mixed	1.24	1.08	1.42	<0.01	1.16	1.02	1.32	0.02
Other	1.08	0.92	1.27	0.33	1.19	1.03	1.38	0.02
Age group, years								
<1	3.48	3.29	3.68	<0.01	1.94	1.79	2.11	<0.01
1–5	1 (ref)				1 (ref)			
6–10	0.46	0.45	0.48	<0.01	0.65	0.62	0.68	<0.01
11–15	0.44	0.42	0.46	<0.01	0.69	0.65	0.73	<0.01
16–20	0.44	0.41	0.46	<0.01	0.72	0.68	0.76	<0.01
21–25	0.43	0.41	0.46	<0.01	0.80	0.75	0.84	<0.01
Main diagnostic group								
Circulatory	1.79	1.56	2.06	<0.01	1.22	1.06	1.39	0.01
Congenital	1 (ref)				1 (ref)			
Gastrointestinal	2.80	2.36	3.32	<0.01	1.32	1.12	1.56	<0.01
Genitourinary	3.05	2.78	3.36	<0.01	1.65	1.51	1.82	<0.01
Haematology	1.84	1.67	2.03	<0.01	1.19	1.08	1.31	<0.01
Metabolic	1.97	1.78	2.19	<0.01	1.34	1.20	1.49	<0.01
Neurology	1.70	1.60	1.81	<0.01	1.33	1.25	1.41	<0.01
Oncology	1.93	1.82	2.06	<0.01	1.01	0.95	1.08	0.68
Perinatal	0.89	0.76	1.05	0.17	0.97	0.83	1.12	0.65
Respiratory	2.29	2.12	2.47	<0.01	1.29	1.19	1.39	<0.01
Other	1.53	1.23	1.90	<0.01	1.23	1.01	1.50	0.04
Deprivation category								
1 (least deprived)	0.72	0.67	0.77	<0.01	0.63	0.59	0.67	<0.01
2	0.75	0.70	0.80	<0.01	0.66	0.62	0.71	<0.01
3	0.82	0.77	0.88	<0.01	0.78	0.73	0.83	<0.01
4	0.95	0.89	1.01	0.10	0.86	0.80	0.91	<0.01
5 (most deprived)	1 (ref)				1 (ref)			
Model parameters								
Degrees of freedom	39				39			
Log likelihood	−91 244.5				−63 549.9			
BIC	182 939.0				127 531.9			

[a]'No. of consultations in year' and 'Year' are continuous variables — incident rate ratios indicate the expected proportional change in outcome rate for one additional consultation and 1 year later in time. A&E = accident and emergency. BIC = Bayesian information criterion.

Multivariable models. Children with an LLC who saw the same GP for two-thirds or more of visits had 10% (95% CI = 6% to 14%) fewer A&E attendances than those seeing the same GP for under half of attendances (Table 1). Children <1 year old had most A&E attendances: 1.94 (95% CI = 1.78 to 2.10) times as many as 1–5-year-olds. Numbers of A&E attendances varied between main diagnostic groups, with those with a genitourinary main diagnosis having most: 1.65 (95% CI = 1.50 to 1.82) times as many as those with a congenital main diagnosis. There was a gradient by deprivation category, with the least deprived having 37% (95% CI = 33% to 41%) fewer A&E attendances than the most deprived.

Children with less regular GP consultations also had increased numbers of A&E attendances, with those with most variation having 5% more (95% CI = 1% to 10%) compared with those with most regular GP consultations (Table 2). The group with too few GP visits to have a coefficient of variation assigned had 9% fewer A&E visits (95% CI = 5% to 12%). The other variables were similar to the previous model.

DISCUSSION

Summary

Overall, the number of face-to-face consultations with a GP had decreased for these children and their families over the period from 2000 to 2015. However, CYP with LLCs who consulted their GP more regularly had fewer emergency hospital admissions and A&E attendances than those with less regular consultations. CYP with an LLC who saw the same GP more often had fewer A&E attendances than those who had less consistency.

Strengths and limitations

This study used a nationally representative sample of primary and secondary care data with robust and transparent statistical techniques. The study is limited by the observational study design and therefore causation cannot be assessed. There are no measures of disease severity or complexity in these data.

The UPC index measure has limitations. Any individuals with <2 consultations per year do not have UPC defined and the group of individuals with two consultations per year have possible values of only 0.5 or 1.0, with 0.5 falling in the middle group in the analyses presented here. This was because including 0.5 in the middle group seemed appropriate for those with a larger number of consultations (for example, for those with two out of four consultations with the same GP). Sensitivity analyses were used with (1) a 2-year period for the outcomes and UPC calculations and (2) requiring three consultations per year for UPC to be defined. Similar associations between UPC and the outcomes were observed in these analyses and they present their own problems, in case (a) the <1-year age group, which differs from other groups, is not defined consistently as individuals cannot be in that age group for 2 years, and in case (b) the group with defined UPC reduces in size.

Comparison with existing literature

There are no comparable studies assessing the regularity of GP visits. However, a US study has shown that children with medical complexity often did not have their annual well child checks, but those who did had reduced hospital admissions.[26] There are similar results for adult patients, where higher continuity of care by GPs has been associated with fewer emergency department attendances[27] and lower mortality.[28]

Implications for research and practice

The 2012 Chief Medical Officer's report[11] recommended that CYP with long-term conditions should have a named GP who coordinates their care. Furthermore, CYP and families have expressed preferences for care to be provided at home[29] and there is policy emphasis on providing care at home and avoiding hospital admissions.[30] The findings of this study highlight the role of GPs and primary care teams as an important area for consideration in the care of this population. Research into the relationship between GPs, CYP with LLCs, and their family members would be of value to better understand these associations. Previous research has suggested that the response of GPs to care of CYP with palliative care needs in cancer can be highly variable, with issues of training and time resource for GPs.[6,31]

These study findings show that the GP attendance rate for CYP with LLCs is decreasing. This may relate to difficulty accessing GP services in a timely fashion and the specialist-led nature of their care. Further consideration of the role and value of GPs and primary care teams in the management of this population is warranted as the number of CYP with LLCs is rising, and more of these CYP are living into young adulthood than ever before. The GP can become the main healthcare provider when these young people are discharged

from paediatric services. GPs are also in a unique position as a healthcare provider for the whole family,[32] which includes bereavement[6,33] if a CYP dies.

Opportunities to see more of CYP with LLCs in primary care already exist, with chronic disease reviews, learning disability checks, and quality improvement initiatives.[34] This study highlights the potential importance of GP continuity of care for CYP with LLCs and their families, alongside care provided by specialist paediatricians. The provision of truly integrated care in the community for CYP with LLCs requires further consideration. Communication between paediatricians and their primary care colleagues would need to improve, including sharing electronic records. Understanding the role that each member of the integrated team can play in the health care of the CYP is also key and worthy of consideration as both the primary care and paediatric workforce requires innovation.[35] In other countries, paediatricians work in primary care providing care to these children in combination with specialists.[36] The evaluation of initiatives in the UK to integrate primary and secondary care for children, including those with chronic or complex conditions, is currently underway (https://www.cyphp.org/).

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Ethical approval

Data access and protocol were approved by the Independent Scientific Advisory Committee (ref: 16_277R). CPRD has ethical approval for observational research using pseudonymised data.

Provenance

Freely submitted; externally peer reviewed.

Competing interests

The authors have declared no competing interests.

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Appendix 2: Supplementary materials for the papers

A2.1 Supplementary materials for paper 2: Transition of children with life-limiting conditions to adult care and healthcare use: a systematic review

A2.1.1 Supplemental results

Supplemental table 1: Studies by outcome (with numerical study ID in parentheses), with direction of effect and effect size. ↓ = decrease ↑= increase ↔=no difference

Study	Condition	Direction of effect	Measure	Sample size	Effect size (95% CI) [per person per year, unless stated]	P-value
Outpatient attendances						
Young 2007/2011 (01)	Cerebral Palsy	↑	Means of groups	1064	0.89 (0.36-1.42)	<0.001
Duguépéroux 2008 (04)	Cystic Fibrosis	↑	Means of groups	68	1.9 (0.8-3.0)	<0.001
Collins 2016 (06)	Cystic Fibrosis	↑	Mean difference	44	2.92	-
Crowley 2018 (07)	Cystic Fibrosis	↓	Means of groups	133	0.4 (0.1-0.7)	0.02
Welsner 2019 (08)	Cystic Fibrosis	↑	Means of groups	39	0.74 (0.01-1.48)	<0.05
Biersteker 2018 (09)	HIV	↓	Medians of groups	25	3.0	0.02
Akchurin 2004 (11)	Renal	↓	Medians of groups	25	0.8	0.75
Pape 2013 (12)	Renal	↓	Means of groups	59	9.0 (3.7-14.3)	<0.001
Blinder 2003 (15)	Sickle Cell	↓	Means of groups	663	0.41 (0.21-0.62)	<0.001
Young 2014 (16)	Spina Bifida	↑	Means of groups	284	0.49 (0.16-0.82)	0.004
Cohen 2016 (17)	Complex chronic conditions	↑	Medians of groups	2520	1.0	<0.001
Inpatient admissions						
Young 2007/2011 (01)	Cerebral Palsy	↓	Means of groups	1064	0.8 (0.3-1.3)	<0.001
Tuchman 2013 (05)	Cystic Fibrosis	↓	Mean difference	1322	0.02 (-0.06-0.10)	0.62
Collins 2016 (06)	Cystic Fibrosis	↑	Mean difference	44	1.71	-
Crowley 2018 (07)	Cystic Fibrosis	↑	Means of groups	133	0.30 (0.11-0.49)	0.002

Welsner 2019 (08)	Cystic Fibrosis	↑	Means of groups	39	1.0 (0.4-1.6)	0.002
Akchurin2004 (11)	Renal	↓	Medians of groups	25	0.25	0.95
Samuel 2014 (13)	Renal	↓	Incidence rate ratio	92	0.71 (0.57-0.90) [IRR]	0.003
Levine 2018 (14)	Renal	↑	Incidence rate ratio	142	3.7 (1.7-8.0) [IRR]	<0.001
Young 2014 (16)	Spina Bifida	↓	Means of groups	284	0.04 (-0.02-0.10)	0.196
Cohen 2016 (17)	Complex chronic conditions	↓	Medians of groups	2520	0	<0.001 (Medians both zero but statistically different)
Emergency inpatient admissions						
Wijlaars 2018 (18)	Blood/cancer – male	↓	Incidence rate ratio	Not known	1.20 (1.17-1.23) [IRR]	<0.001
	Blood/cancer - female	↑	Incidence rate ratio	Not known	0.92 (0.89-0.96)[IRR]	<0.001
Emergency Department visits						
Young 2007/2011 (01)	Cerebral Palsy	↑	Means of groups	1064	0.55 (0.22-0.88)	<0.001
Levine 2018 (14)	Renal	↓	Incidence rate ratio	142	0.35 [IRR]	-
Blinder 2003 (15)	Sickle Cell	↑	Means of groups	663	1.44 (0.59-2.29)	<0.001
Young 2014 (16)	Spina Bifida	↑	Means of groups	284	0.07 (0.03-0.11)	<0.001
Cohen 2016 (17)	Complex chronic conditions	↔	Medians of groups	2520	0	0.14
Inpatient bed days						
Young 2007/2011 (01)	Cerebral Palsy	↓	Means of groups	1064	0.37 (0.15-0.59)	<0.001
Collins 2016 (06)	Cystic Fibrosis	↑	Mean difference	44	1.71	-
Levine 2018 (14)	Renal	↑	Incidence rate ratio	142	4.14 (0.76-22.23) [IRR]	≤0.1
Blinder 2003 (15)	Sickle Cell	↑	Means of groups	663	20.48 8.33-32.63)	<0.001
Intravenous antibiotic courses						

Duguépéroux 2008 (04)	Cystic Fibrosis	↑	Means of groups	68	0.3 (-7.9-9.7)	0.333
Tuchman 2013 (05)	Cystic Fibrosis	↑	Mean difference	1322	0.04 (-0.03-0.11)	0.256
Collins 2016 (06)	Cystic Fibrosis	↑	Mean difference	44	1.96	-
Physiotherapy						
Liljenquist 2018 (02)	Cerebral Palsy	↓	% of persons receiving therapy	35290	0.35 (0.34-0.36) [OR]	<0.001
Roquet 2018 (03)	Cerebral Palsy	↔	% of persons receiving therapy	54	1 [OR]	-
Duguépéroux 2008 (04)	Cystic Fibrosis	↓	% of persons receiving therapy	68	0.88 (0.40-1.91) [OR]	0.855
HIV care						
Gray 2019 (10)	HIV	↓	% of persons receiving care	3111	0.61 (0.51-0.72) [OR]	<0.001
General practitioner visits						
Roquet 2018 (03)	Cerebral Palsy	↑	% of persons having a visit	54	1.2 (0.3-4.5) [OR]	0.77
Overall healthcare costs						
Blinder 2003 (15)	Sickle Cell (patients receiving iron chelation therapy)	↑	Means of groups	450	1916 (-1938-5770) [$US]	0.335
	Sickle Cell (patients not receiving iron chelation therapy)	↑	Means of groups	663	7749 (3151-12345) [$US]	<0.001
Cohen 2016 (17)	Complex chronic conditions	↓	Medians of groups	2520	893 [$CAN]	<0.001

A2.1.2 Search strategy

Concepts

LLC AND Child/young adult AND Transition

Fourth concept, health and social care, not searched

Basis of search strategies

LLC

Based on two searches developed by YHEC (Arber 2014).

Child/young adult

Developed from McPheeters, Davis et al. (2014), Rachas, Tuppin et al. (2018), Prior, McManus et al. (2014), Heery, Sheehan et al. (2015), Leclercq, Leeflang et al. (2013), National Institute for Health and Care Excellence (2016) and Association pour l'avancement des sciences et des techniques de la documentation (2018).

Transition

Developed from McPheeters, Davis et al. (2014), Rachas, Tuppin et al. (2018), Prior, McManus et al. (2014), Heery, Sheehan et al. (2015) and National Institute for Health and Care Excellence (2016).

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MEDLINE (Ovid)

Concepts:

1. LLC: lines 1-583
2. Child/young adult: lines 584-595
3. Transition: lines 596-607

1	Creutzfeldt-Jakob Syndrome/
2	(creutzfeldt-jakob$ or jakob-creutzfeldt$ or cjd or spongiform encephalopath$).ti,ab,kf.
4	(subacute sclerosing panencephalit$ or sub-acute sclerosing panencephalit$ or sspe or subacute sclerosing leukoencephalit$ or sub-acute sclerosing leukoencephalit$ or van bogaert$ leukoencephalit$ or measles inclusion body encephalit$ or mibe).ti,ab,kf.
5	beta-Thalassemia/
6	(beta adj (thalass?emi$ or thalas?emi$)).ti,ab,kf.
7	((thalass?emi$ or thalas?emi$) adj major).ti,ab,kf.
8	exp Anemia, Aplastic/
9	((hypoplastic or aplastic) adj an?emi$).ti,ab,kf.
10	(medullary adj3 hypoplas$).ti,ab,kf.
11	exp Neutropenia/
12	((severe or chronic$) adj3 neutropeni$).ti,ab,kf.
13	immunologic deficiency syndromes/ or acquired immunodeficiency syndrome/
14	(immun$ deficiency adj (syndrome$ or disease$ or disorder$)).ti,ab,kf.
15	(immunodeficiency adj (syndrome$ or disease$ or disorder$)).ti,ab,kf.
16	DiGeorge Syndrome/
17	(digeorge$ or di george$ or sedlackova$ or opitz g-bbb or velocardiofacial or velo-cardiofacial or velo-cardio-facial or shprintzen$ or ctaf).ti,ab,kf.
18	((deletion or vcf or pharyngeal pouch or thymic aplasia or anomaly face) adj (syndrome$ or disease$ or disorder$)).ti,ab,kf.
19	Common Variable Immunodeficiency/
20	((common variable or late onset) adj3 (immunodeficienc$ or immune deficienc$ or immunoglobulin deficienc$ or hypogammaglobulin$)).ti,ab,kf.
21	acquired hypogammaglobulin$.ti,ab,kf.
22	Cryoglobulinemia/
23	cryoglobulin?em$.ti,ab,kf.
24	Polyendocrinopathies, Autoimmune/
25	((autoimmune or failure$) adj3 (polyglandular$ or polyendocrin$)).ti,ab,kf.
26	Progeria/
27	(progeria or hutchinson-gilford$).ti,ab,kf.
28	Tyrosinemias/
29	tyrosin?em$.ti,ab,kf.
30	Maple Syrup Urine Disease/
31	(maple syrup urine or msud).ti,ab,kf.
32	branched chain.ti,ab,kf.
33	(bckd adj5 (deficienc$ or ketoacid$ or keto-acid$)).ti,ab,kf.
34	hyperleucine-isoleucin$.ti,ab,kf.

35	Methylmalonic Acid/
36	(methylmalonic acid?emi$ or methylmalonic aciduri$ or methyl malonic acid?emi$ or methyl malonic aciduri$).ti,ab,kf.
37	Propionic Acidemia/
38	(propionic acid?em$ or propionic acidur$ or propionyl-CoA carboxylase deficienc$ or ketotic glycin?em$).ti,ab,kf.
39	Adrenoleukodystrophy/
40	(adrenoleukodystroph$ or x-ald or schilder-addison$ or addison-schilder$ or adrenomyeloneuropath$).ti,ab,kf.
41	Carnitine O-Palmitoyltransferase/
42	((carnitine palmityltransferase or carnitine palmitoyltransferase or carnitine o-palmityltransferase or carnitine o-palmitoyltransferase) adj3 deficienc$).ti,ab,kf.
43	Fanconi Syndrome/
44	(fanconi$ adj (syndrome$ or disease$ or disorder$)).ti,ab,kf.
45	(ocular adj3 (renal or kidney)).ti,ab,kf.
46	Cystinosis/
47	(cystinos$ or cystine storage or cystine diathes$ or cystine disease$).ti,ab,kf.
48	Oculocerebrorenal Syndrome/
49	((lowe or lowes or oculocerebrorenal or cerebrooculorenal or cerebro-oculo-renal) adj3 (syndrome$ or disease$ or disorder$)).ti,ab,kf.
50	Metalloproteins/df
51	Molybdenum/df
52	(molybdenum cofactor deficien$ or molybdenum co-factor deficien$).ti,ab,kf.
53	Oxidoreductases Acting on Sulfur Group Donors/df
54	Sulfite Oxidase/df
55	((sulphite$ or sulfite$) adj3 oxidase deficien$).ti,ab,kf.
56	Argininosuccinic Acid/
57	(argininosuccinic acidur$ or argininosuccinic acid?emi$).ti,ab,kf.
58	Citrullinemia/
59	(citrullin?emi$ or citrullinuri$).ti,ab,kf.
60	Amino Acid Metabolism, Inborn Errors/
61	(glutaric acid?emi$ or glutaric aciduri$).ti,ab,kf.
62	Hyperglycinemia, Nonketotic/
63	(glycine encephalopath$ or non-ketotic hyperglycin?emi$ or nonketotic hyperglycin?emi$).ti,ab,kf.
64	Hyperargininemia/
65	(arginin?emi$ or arginase deficien$ or hyperarginin?emi$).ti,ab,kf.
66	Renal Aminoacidurias/
67	(aminoaciduri$ or aminoacid?emi$).ti,ab,kf.
68	exp glycogen storage disease/
69	(glycogen storage adj (disease$ or syndrome$ or disorder$)).ti,ab,kf.
70	(pompe$ adj (disease$ or syndrome$ or disorder$)).ti,ab,kf.
71	Galactosemias/
72	galactos?emi$.ti,ab,kf.
73	Pyruvate Dehydrogenase Complex Deficiency Disease/
74	(pyruvate dehydrogenase adj3 deficien$).ti,ab,kf.
75	(oxalosis and (renal or kidney$)).ti,ab,kf.
76	exp Gangliosidoses/
77	gangliosidos$.ti,ab,kf.
78	(sandhoff$ adj (disease$ or syndrome$ or disorder$)).ti,ab,kf.

79	tay sach$.ti,ab,kf.
80	Mucolipidoses/
81	mucolipidos$.ti,ab,kf.
82	Canavan Disease/
83	(canavan$ leucodystroph$ or aspartoacylase deficien$ or aminoacylase 2 deficien$).ti,ab,kf.
84	((canavan$ or canavan-van bogaert-bertrand$) adj (disease$ or syndrome$ or disorder$)).ti,ab,kf.
85	Gaucher Disease/
86	(gaucher$ adj (disease$ or syndrome$ or disorder$)).ti,ab,kf.
87	(glucocerebrosidase deficien$ or glucosylceramidase deficien$).ti,ab,kf.
88	Leukodystrophy, Metachromatic/
89	(metachromatic leukodystroph$ or arylsulfatase A deficien$ or metachromic leukodystroph$).ti,ab,kf.
90	exp Niemann-Pick Diseases/
91	(niemann-pick$ or sphingomyelinase deficien$).ti,ab,kf.
92	Sphingolipidoses/
93	sphingolipidos$.ti,ab,kf.
94	Fabry Disease/
95	(fabry$ adj (disease$ or syndrome$ or disorder$)).ti,ab,kf.
96	(angiokeratoma corporis diffusum or alpha-galactosidase A deficien$).ti,ab,kf.
97	Leukodystrophy, Globoid Cell/
98	(krabbe$ adj (disease$ or syndrome$ or disorder$)).ti,ab,kf.
99	(globoid cell leukodystroph$ or galactosylceramide lipidos$ or galactosylcerebrosidase deficien$ or galactosylceramidase deficien$).ti,ab,kf.
100	Farber Lipogranulomatosis/
101	(farber$ adj (disease$ or syndrome$ or disorder$)).ti,ab,kf.
102	(farber$ lipogranulomatos$ or ceramidase deficien$ or fibrocytic dysmucopolysaccharidos$).ti,ab,kf.
103	Pelizaeus-Merzbacher Disease/
104	pelizaeus-merzbacher$.ti,ab,kf.
105	Sulfatases/df
106	Multiple Sulfatase Deficiency Disease/
107	(sulfatase deficien$ or sulphatase deficien$ or mucosulfatidos$).ti,ab,kf.
108	(austin$ adj (disease$ or syndrome$ or disorder$)).ti,ab,kf.
109	sulfatidosis/
110	sulfatidos$.ti,ab,kf.
111	Sea-Blue Histiocyte Syndrome/
112	sea-blue histiocyt$.ti,ab,kf.
113	Neuronal Ceroid-Lipofuscinoses/
114	(batten$ adj (disease$ or syndrome$ or disorder$)).ti,ab,kf.
115	(neuronal ceroid lipofuscinos$ or santavuori-haltia$ or jansky-bielschowsky$ or bielschowsky-jansky$).ti,ab,kf.
116	(kuf$ adj (disease$ or syndrome$ or disorder$)).ti,ab,kf.
117	spielmeyer vogt$.ti,ab,kf.
118	Xanthomatosis, Cerebrotendinous/
119	((cerebrotendineous or cerebrotendinous or cerebrotendious or cerebral) adj3 (xanthomatos$ or cholesteros$)).ti,ab,kf.
120	bogaert-scherer-epstein$.ti,ab,kf.
121	Wolman Disease/

122	(wolman$ adj (disease$ or syndrome$ or disorder$)).ti,ab,kf.
123	lysosomal acid lipase deficien$.ti,ab,kf.
124	exp Mucopolysaccharidoses/
125	mucopolysaccharidos$.ti,ab,kf.
126	(hurler$ adj2 (syndrome$ or disease$ or disorder$)).ti,ab,kf.
127	(hunter$ adj2 (syndrome$ or disease$ or disorder$)).ti,ab,kf.
128	(MPS1 or MPS2 or MPS3 or MPS4 or MPS5 or MPS6 or MPS7 or MPS-1 or MPS-2 or MPS-3 or MPS-4 or MPS-5 or MPS-6 or MPS-7 or MPSI or MPSII or MPSIII or MPSIV or MPSV or MPSVI or MPSVII or MPS-I or MPS-II or MPS-III or MPS-IV or MPS-V or MPS-VI or MPS-VII).ti,ab,kf.
129	(beta glucuronidase deficien$ or sly syndrome$ or sly disorder$ or sly disease$).ti,ab,kf.
130	(maroteaux-lamy$ or marotaeux-lamy$ or polydystrophic dwarfism).ti,ab,kf.
131	(morquio$ or moriquio$ or beta galactosidase deficien$).ti,ab,kf.
132	(sanfilippo$ or sanfillipo$).ti,ab,kf.
133	Mucolipidoses/
134	(mucolipidos$ or pseudo-hurler$ or pseudohurler$).ti,ab,kf.
135	((inclusion-cell or i-cell) adj (disease$ or syndrome$ or disorder$)).ti,ab,kf.
136	Fucosidosis/
137	(fucosidos$ or fucidos$).ti,ab,kf.
138	"Congenital Disorders of Glycosylation"/
139	((cdg or ctg) adj (disease$ or disorder$ or syndrome$)).ti,ab,kf.
140	(carbohydrate-deficient glycoprotein adj (disease$ or disorder$ or syndrome$)).ti,ab,kf.
141	(congenital disorder$ adj3 glycosylation).ti,ab,kf.
142	Lesch-Nyhan Syndrome/
143	juvenile gout.ti,ab,kf.
144	Menkes Kinky Hair Syndrome/
145	menkes$.ti,ab,kf.
146	((copper transport or steely hair or kinky hair) adj (disease$ or syndrome$ or disorder$)).ti,ab,kf.
147	alpha 1-Antitrypsin Deficiency/
148	(antitrypsin deficien$ or A1AD).ti,ab,kf.
149	(AAT deficien$ or alpha-1 protease deficien$).ti,ab,kf.
150	bisalbumin?emi$.ti,ab,kf.
151	Lipodystrophy, Congenital Generalized/
152	(congenital generali?ed lipodystroph$ or berardinelli$ or bernardnelli$).ti,ab,kf.
153	Landau-Kleffner Syndrome/
154	(landau-kleffner$ or infantile acquired aphasia$ or acquired epileptic aphasia$).ti,ab,kf.
155	(aphasia$ adj5 convulsive).ti,ab,kf.
156	Rett Syndrome/
157	(rett$ adj (syndrome$ or disease$ or disorder$)).ti,ab,kf.
158	cerebroatrophic hyperammon?emi$.ti,ab,kf.
159	Huntington Disease/
160	huntington$.ti,ab,kf.
161	exp Spinocerebellar Ataxias/
162	((nyhan$ or kelley-seegmiller$) adj (syndrome$ or disorder$ or disease$)).ti,ab,kf.

163	(spinocerebellar ataxia$ or ataxia$ telangiectasia$ or louis-bar$ syndrome$ or louis-bar$ disease$ or louis-bar$ disorder$ or machado-joseph$ or joseph$ disease$ or joseph$ disorder$ or joseph$ syndrome$).ti,ab,kf.
164	Friedreich Ataxia/
165	((friedreich$ or friedrich$) adj3 ataxia$).ti,ab,kf.
166	spinocerebellar degenerat$.ti,ab,kf.
167	"Spinal Muscular Atrophies of Childhood"/
168	(spinal muscular atroph$ or werdnig hoffman$).ti,ab,kf.
169	(dubowitz$ or kugelberg-welander$).ti,ab,kf.
170	Bulbar Palsy, Progressive/
171	(fazio-londe$ or faziolonde$ or progressive bulbar pals$).ti,ab,kf.
172	parkinson disease/ or parkinson disease, secondary/
173	(parkinson$ or hypokinetic rigid syndrome$ or hypokinetic rigid disease$ or hypokinetic rigid disorder$ or paralysis agitan$ or shaking pals$).ti,ab,kf.
174	Pantothenate Kinase-Associated Neurodegeneration/
175	(pantothenate kinase-associated neurodegenerat$ or PKAN or hallervorden-spatz$).ti,ab,kf.
176	((neurodegeneration adj3 brain iron accumulation) or NBIA$1).ti,ab,kf.
177	Olivopontocerebellar Atrophies/
178	(olivopontocerebellar atroph$ or OPCA or olivopontocerebellar degenerat$).ti,ab,kf.
179	(multiple system atrophy adj5 cerebellar).ti,ab,kf.
180	"Diffuse Cerebral Sclerosis of Schilder"/
181	(alper$ adj (disease$ or syndrome$ or disorder$)).ti,ab,kf.
182	(progressive sclerosing poliodystroph$ or progressive infantile poliodystroph$).ti,ab,kf.
183	(diffuse cerebral sclerosis adj5 schilder$).ti,ab,kf.
184	Leigh Disease/
185	(leigh$ adj (syndrome$ or disease$ or disorder$)).ti,ab,kf.
186	(subacute necrotizing encephalomyelopath$ or subacute necrotising encephalomyelopath$ or sub-acute necrotizing encephalomyelopath$ or sub-acute necrotising encephalomyelopath$ or SNEM).ti,ab,kf.
187	(aicardi-gouti?res or aicardia-gouti?res).ti,ab,kf.
188	(worster-drought$ or congenital suprabulbar pares$).ti,ab,kf.
189	multiple sclerosis/ or multiple sclerosis, chronic progressive/ or multiple sclerosis, relapsing-remitting/
190	(multiple sclerosis or disseminated sclerosis or encephalomyelitis disseminata$).ti,ab,kf.
191	(demyelinating adj (disease$ or syndrome$ or disorder$)).ti,ab,kf.
192	exp Epilepsies, Myoclonic/
193	myoclonic epileps$.ti,ab,kf.
194	((lafora$ or merrf$ or unverricht-lundborg$ or janz$) adj (disease$ or syndrome$ or disorder$)).ti,ab,kf.
195	lennox-gastaut$.ti,ab,kf.
196	(lennox$ adj (syndrome$ or disease$ or disorder$)).ti,ab,kf.
197	Spasms, Infantile/
198	(west$ adj (syndrome$ or disease$ or disorder$)).ti,ab,kf.
199	Epilepsia Partialis Continua/
200	(epilepsia partialis continua or kojevnikov$ or epilepsia partialis continuoa or kozhevnikof$).ti,ab,kf.

201	Charcot-Marie-Tooth Disease/
202	(charcot-marie-tooth$ or peroneal muscular atroph$).ti,ab,kf.
203	(progressive neuropathic muscular atroph$ or hereditary peroneal nerve dysfunction$ or peroneal neuropath$).ti,ab,kf.
204	"Hereditary Sensory and Motor Neuropathy"/
205	(hereditary sensory adj3 motor neuropath$).ti,ab,kf.
206	(hereditary motor adj3 sensory neuropath$).ti,ab,kf.
207	Refsum Disease, Infantile/
208	Peroxisomal Disorders/
209	(infantile refsum or infantile phytanic acid storage).ti,ab,kf.
210	Myasthenic Syndromes, Congenital/
211	congenital myasth?eni$.ti,ab,kf.
212	Muscular Dystrophy, Duchenne/
213	(duchenne muscular dystroph$ or dmd).ti,ab,kf.
214	exp Muscular Dystrophies, Limb-Girdle/
215	(limb-girdle or erb$ muscular dystroph$).ti,ab,kf.
216	(sarcoglycanopath$ or sarcoglycaopath$).ti,ab,kf.
217	Osteochondrodysplasias/
218	(osteochondrodysplas$ or schwartz-jampel or chondrodystrophi$ myotoni$ or myotoni$ chondrodystrophi$).ti,ab,kf.
219	Myotonia Congenita/
220	(congenita$ myotoni$ or myotoni$ congenita$).ti,ab,kf.
221	(thomsen$ adj (disease$ or disorder$ or syndrome$)).ti,ab,kf.
222	((recessive adj3 myotoni$) or becker$ myotoni$).ti,ab,kf.
223	Isaacs Syndrome/
224	(isaac$ adj (syndrome$ or disease$ or disorder$)).ti,ab,kf.
225	neuromyotoni$.ti,ab,kf.
226	Myotonic Disorders/
227	(paramyotoni$ congenita$ or congenita$ paramyotoni$).ti,ab,kf.
228	(eulenburg$ adj (disease$ or syndrome$ or disorder$)).ti,ab,kf.
229	(myotoni$ adj (disease$ or disorder$ or syndrome$)).ti,ab,kf.
230	pseudomyotoni$.ti,ab,kf.
231	exp Myopathies, Structural, Congenital/
232	(congenital adj3 myopath$).ti,ab,kf.
233	myopathycongenital.ti,ab,kf.
234	((nemaline or rod) adj3 myopath$).ti,ab,kf.
235	((central core or mini-core or minicore or multicore or multi-core) adj (disease$ or disorder$ or syndrome$ or myopath$)).ti,ab,kf.
236	fiber type disproportion.ti,ab,kf.
237	fibre type disproportion.ti,ab,kf.
238	Muscular Dystrophies/cn
239	(congenital$ adj5 muscular dystroph$).ti,ab,kf.
240	((centronuclear or myotubular) adj myopath$).ti,ab,kf.
241	exp Mitochondrial Myopathies/
242	(mitochondrial myopath$ or mitochondrial encephalomyopath$ or chronic progressive external ophthalmopleg$).ti,ab,kf.
243	((melas or kearns-sayre$) adj (syndrome$ or disease$ or disorder$)).ti,ab,kf.
244	Quadriplegia/ and spastic$.ti,ab,kf.
245	(spastic quadriplegi$ or spastic tetraplegi$).ti,ab,kf.
246	Reye Syndrome/

247	(reye$ adj (syndrome$ or disease$ or disorder$)).ti,ab,kf.
248	multiple pterygium.ti,ab,kf.
249	Hypertension, Pulmonary/ and primary$.ti,ab,kf.
250	((primary pulmonary or precapillary pulmonary or idiopathic pulmonary) adj (hypertension or ht or arterial hypertension)).ti,ab,kf.
251	((primary bronchopulmonary or precapillary bronchopulmonary or idiopathic bronchopulmonary) adj (hypertension or ht or arterial hypertension)).ti,ab,kf.
252	((primary lung or precapillary lung or idiopathic lung) adj (hypertension or ht or arterial hypertension)).ti,ab,kf.
253	ipah.ti,ab,kf.
254	Cardiomyopathy, Dilated/
255	((congestive or dilated) adj cardiomyopath$).ti,ab,kf.
256	exp Cardiomyopathy, Hypertrophic/
257	(hypertrophic adj cardiomyopath$).ti,ab,kf.
258	Cardiomyopathies/cn
259	(congenital adj3 cardiomyopath$).ti,ab,kf.
260	Cardiomyopathy, Restrictive/
261	(restrictive cardiomyopath$ or obliterative cardiomyopath$ or constrictive cardiomyopath$).ti,ab,kf.
262	exp Pulmonary Fibrosis/
263	(pulmonary fibros$ or lung fibros$ or bronchopulmonary fibros$ or fibrosing alveolit$ or interstitial pneumonit$).ti,ab,kf.
264	Respiratory Insufficiency/
265	(respiratory adj (failure$ or insufficienc$)).ti,ab,kf.
266	"Cystic Adenomatoid Malformation of Lung, Congenital"/
267	((cystic lung or cystic pulmonary or cystic bronchopulmonary) adj (disease$ or disorder or syndrome$)).ti,ab,kf.
268	(bronchogenic cyst$ or bronchopulmonary foregut malformation$).ti,ab,kf.
269	cystic adenomatoid malformation$.ti,ab,kf.
270	lobar emphysem$.ti,ab,kf.
271	(pulmonary sequestration$ or bronchopulmonary sequestration$ or lung sequestration$ or extralobar sequestration$ or extra-lobar sequestration$ or intralobar sequestration$ or intra-lobar sequestration$).ti,ab,kf.
272	pulmolithias$.ti,ab,kf.
273	exp Liver Failure/
274	((liver$1 or hepatic) adj3 fail$).ti,ab,kf.
275	exp Liver Cirrhosis/
276	(cirrhosis adj3 liver$1).ti,ab,kf.
277	Hepatic Veno-Occlusive Disease/
278	((veno-occlusive or venous occlusive) adj (disease$ or syndrome$ or disorder$)).ti,ab,kf.
279	Exocrine Pancreatic Insufficiency/
280	(swachman-diamond or shwachman-bodian or schwachmann-diamond or shwachmann-bodian).ti,ab,kf.
281	Wegener Granulomatosis/
282	wegener$ granulomatos$.ti,ab,kf.
283	(granulomatos$ adj3 polyangiit$).ti,ab,kf.
284	Osteolysis, Essential/
285	essential osteolys$.ti,ab,kf.

286	((gorham$ or gorham-stout$ or vanishing bone or phantom bone) adj (disease$ or syndrome$ or disorder)).ti,ab,kf.
287	((arc or arthrogryposis renal dysfunction cholestasis) adj (disease$ or syndrome$ or disorder)).ti,ab,kf.
288	Cerebral Hemorrhage/cn
289	Cerebral Hemorrhage, Traumatic/
290	Cerebral Hemorrhage/ and Birth Injuries/
291	(cerebral h?emorrhage$ and (birth$ adj3 injur$)).ti,ab,kf.
292	Asphyxia Neonatorum/
293	asphyxia neonatorum.ti,ab,kf.
294	((perinatal$ or neonatal$ or birth$) adj3 asphyxia$).ti,ab,kf.
295	Rubella Syndrome, Congenital/
296	congenital rubella.ti,ab,kf.
297	exp Cytomegalovirus Infections/cn
298	(congenital adj (cytomegalovirus$ or cmv)).ti,ab,kf.
299	Chickenpox/cn
300	exp Herpes Zoster/cn
301	Herpesvirus 3, Human/ and congenital$.ti,ab,kf.
302	((congenital or fetal or foetal) adj3 (varicella$ or chicken pox$ or VZV)).ti,ab,kf.
303	Toxoplasmosis, Congenital/
304	congenital toxoplasmos$.ti,ab,kf.
305	exp Hypoxia, Brain/
306	((brain$ or cerebral) adj3 hypoxi$).ti,ab,kf.
307	Renal Insufficiency/cn
308	Acute Kidney Injury/cn
309	Renal Insufficiency, Chronic/cn
310	Kidney Failure, Chronic/cn
311	(congenital$ adj3 (kidney failure$ or renal failure$ or kidney insufficienc$ or renal insufficienc$)).ti,ab,kf.
312	(congenital$ adj3 (kidney disease$ or renal disease$)).ti,ab,kf.
313	Anencephaly/
314	(anencephal$ or meroanencephal$ or craniorachischis$).ti,ab,kf.
315	(aprosencephal$ adj3 open cranium).ti,ab,kf.
316	Encephalocele/
317	(encephalocele$ or cranium bifidum).ti,ab,kf.
318	Dandy-Walker Syndrome/
319	dandy-walker$.ti,ab,kf.
320	Acrocallosal Syndrome/
321	(acrocallosal or acro-callosal or acrocolossal or acro colossal).ti,ab,kf.
322	Aicardi Syndrome/
323	(aicardi$ adj (syndrome$ or disease$ or disorder$)).ti,ab,kf.
324	Holoprosencephaly/
325	(holoprosencephal$ or arhinencephal$ or holosprosencephal$).ti,ab,kf.
326	Hydranencephaly/
327	(hydranencephal$ or hydrancephal$ or hydroanencephal$).ti,ab,kf.
328	exp Lissencephaly/
329	Microcephaly/
330	(lissencephal$ or walker-warburg$ or miller-dieker$ or norman-robert$ or microlissencephal$).ti,ab,kf.

331	((fukuyama$ or muscle-eye-brain) adj (syndrome$ or disease$ or disorder$)).ti,ab,kf.
332	"Malformations of Cortical Development"/
333	(microgyria$ or microgyrus or micro-gyria$ or micro-gyrus).ti,ab,kf.
334	(pachygyria$ or pachgyria$).ti,ab,kf.
335	agyria$.ti,ab,kf.
336	Septo-Optic Dysplasia/
337	((septo-optic or septooptic) adj dysplas$).ti,ab,kf.
338	de morsier$.ti,ab,kf.
339	(schizencephal$ or schizzencephal$).ti,ab,kf.
340	Arnold-Chiari Malformation/
341	chiari$ malformation$.ti,ab,kf.
342	Truncus Arteriosus, Persistent/
343	(truncus or common arterial trunk$).ti,ab,kf.
344	"Transposition of Great Vessels"/
345	((transposition$ or dextrotransposition$ or dtransposition$ or levotransposition$ or ltransposition$) adj3 (great arter$ or main arter$ or aorta$ or pulmonary arter$ or great vessel$ or main vessel$)).ti,ab,kf.
346	(dextro-tga or d-tga or levo-tga or l-tga).ti,ab,kf.
347	(double inlet adj3 ventricle$).ti,ab,kf.
348	DILV.ti,ab,kf.
349	single ventricle$.ti,ab,kf.
350	Heart Defects, Congenital/ and Atrial Appendage/
351	(isomerism adj3 atrial appendage$).ti,ab,kf.
352	(aspleni$ or polyspleni$ or poly-spleni$).ti,ab,kf.
353	"Tetralogy of Fallot"/
354	(tetralogy adj3 fallot$).ti,ab,kf.
355	Eisenmenger Complex/
356	(eisenmenger$ or tardive cyanos$ or eisenmeyer$).ti,ab,kf.
357	(pentalogy adj3 fallot$).ti,ab,kf.
358	Pulmonary Atresia/
359	((pulmonary or bronchopulmonary or lung$) adj3 atresia$).ti,ab,kf.
360	Tricuspid Atresia/
361	((tricuspid or tri) adj3 atresia$).ti,ab,kf.
362	Ebstein Anomaly/
363	(ebstein$ adj (anomal$ or malformation$)).ti,ab,kf.
364	Hypoplastic Left Heart Syndrome/
365	(hypoplastic left heart adj (syndrome$ or disease$ or disorder$)).ti,ab,kf.
366	((aortic or aorta$) adj3 atresia$).ti,ab,kf.
367	(mitral adj3 atresia$).ti,ab,kf.
368	((absence$ or absent$) adj3 (aorta$ or aortic)).ti,ab,kf.
369	(aplas$ adj3 (aorta$ or aortic)).ti,ab,kf.
370	exp Aortic Aneurysm/cn
371	(((aorta$ or aortic) adj3 aneurys$) and congenital$).ti,ab,kf.
372	(hypoplas$ adj3 (aorta$ or aortic)).ti,ab,kf.
373	(convulsion$ adj3 (aorta$ or aortic)).ti,ab,kf.
374	(persistent right adj3 (aorta$ or aortic)).ti,ab,kf.
375	((anomalous pulmonary venous or anamolous pulmonary venous) adj (connection or drainage or return)).ti,ab,kf.
376	((absence$ or absent$) adj3 vena$ cava$).ti,ab,kf.

377	(persistent left adj3 cardinal vein$).ti,ab,kf.
378	Scimitar Syndrome/
379	((scimitar$ or pulmonary venolobar) adj (syndrome$ or disease$ or disorder$)).ti,ab,kf.
380	(arteriovenous malformations/ or intracranial arteriovenous malformations/) and bilateral.ti,ab,kf.
381	((bilateral AV or bilateral arteriovenous or bilateral arterio-venous) adj3 malform$).ti,ab,kf.
382	((trachea$ or windpipe$ or wind-pipe$) adj3 atresia$).ti,ab,kf.
383	Tracheal Stenosis/
384	((trachea$ or laryngotrachea$ or glottic or subglottic or sub-glottic) adj3 stenosis).ti,ab,kf.
385	Bronchopulmonary Dysplasia/
386	((lung$ or pulmonary or bronchopulmonary) adj3 (hypoplas$ or dysplas$)).ti,ab,kf.
387	((absence$ or absent$) adj3 (esophag$ or oesophag$ or foodpipe or food-pipe$ or gullet$)).ti,ab,kf.
388	Intestinal Atresia/
389	(duoden$ adj3 atresia$).ti,ab,kf.
390	((absence$ or absent$) adj3 (intestin$ or gastrointestin$)).ti,ab,kf.
391	((intestin$ or gastrointestin$) adj3 atresia$).ti,ab,kf.
392	((intestin$ or gastrointestin$) adj3 stenos$).ti,ab,kf.
393	(cloaca$ adj3 (abnor$ or malform$ or anomal$)).ti,ab,kf.
394	(cloaca$ adj3 exopthalmo$).ti,ab,kf.
395	Biliary Atresia/
396	(biliary adj3 atresia$).ti,ab,kf.
397	(extrahepatic ductopen$ or extra-hepatic ductopen$ or progressive obliterative cholangiopath$).ti,ab,kf.
398	(biliary adj3 hypoplas$).ti,ab,kf.
399	(alagille$ adj3 atresia$).ti,ab,kf.
400	((absence$ or absent$) adj3 kidney$).ti,ab,kf.
401	(potter$ adj (sequence$ or syndrome$ or disease$ or disorder$)).ti,ab,kf.
402	Oligohydramnios/
403	oligohydramn$.ti,ab,kf.
404	Multicystic Dysplastic Kidney/
405	((kidney$ or renal) adj3 dysplas$).ti,ab,kf.
406	((meckel$ or meckelgruber$ or gruber$) adj (syndrome$ or disease$ or disorder$)).ti,ab,kf.
407	dysencephalia splanchnocystica$.ti,ab,kf.
408	(pena-shokeir$ or penn-shokeir$).ti,ab,kf.
409	(larsen$ adj (syndrome$ or disease$ or disorder$)).ti,ab,kf.
410	Acrocephalosyndactylia/
411	acrocephalosyndactyl$.ti,ab,kf.
412	(pfeiffer$ adj (syndrome$ or disease$ or syndrome$)).ti,ab,kf.
413	Short Rib-Polydactyly Syndrome/
414	short rib$1.ti,ab,kf.
415	(saldino-noonan$ or majewski$ or verma-naumoff$ or beemer-langer$).ti,ab,kf.
416	(jeune$ adj (syndrome$ or disease$ or disorder$)).ti,ab,kf.
417	asphyxiating thoracic dysplas$.ti,ab,kf.
418	exp Chondrodysplasia Punctata/

419	chondrodysplasia punctata$.ti,ab,kf.
420	((conradi$ or h?nermann$ or happle$) adj3 (syndrome$ or disease$ or disorder$)).ti,ab,kf.
421	Osteogenesis Imperfecta/
422	osteogenesis imperfecta.ti,ab,kf.
423	((brittle bone or lobstein$) adj (disease$ or disorder$ or syndrome$)).ti,ab,kf.
424	Osteochondrodysplasias/
425	(spondyloepimetaphyseal or spondyloepiphyseal or spendylo metaphyseal).ti,ab,kf.
426	Hernia, Umbilical/
427	(omphalocele$ or omphalocoele$ or exomphalos).ti,ab,kf.
428	(hernia$ adj3 umbilic$).ti,ab,kf.
429	Gastroschisis/
430	gastroschis$.ti,ab,kf.
431	Ichthyosis, Lamellar/
432	(lamellar$ adj3 ichthyos$).ti,ab,kf.
433	((harlequin$ or harloquin$) adj3 (ichthyos$ or baby or babies or f?etus$)).ti,ab,kf.
434	(ichthyosis congenita$ or ichthyosis fetalis or keratosis diffusa fetalis).ti,ab,kf.
435	exp Epidermolysis Bullosa/
436	epidermolysis bullosa$.ti,ab,kf.
437	(johanson-blizzard$ or johanna-blizzard$).ti,ab,kf.
438	Xeroderma Pigmentosum/
439	xeroderma pigmentosum.ti,ab,kf.
440	Ectodermal Dysplasia/
441	lacrimo-auriculo-dento-digital.ti,ab,kf.
442	ectodermal dysplas$.ti,ab,kf.
443	((ladd or eec) adj (syndrome$ or disease$ or disorder$)).ti,ab,kf.
444	Sturge-Weber Syndrome/
445	(sturge-weber or encephalotrigeminal angiomatos$).ti,ab,kf.
446	Fetal Alcohol Spectrum Disorders/
447	f?etal alcohol.ti,ab,kf.
448	Pierre Robin Syndrome/
449	pierre robin$.ti,ab,kf.
450	Acrocephalosyndactylia/
451	(acrocephalosyndact$ or acrocephalopolysyndact$).ti,ab,kf.
452	((apert$ or crouzon$ or saethre-chotzen$ or noack$ or carpenter$ or sakati-nyhan-tisdale$ or goodman$) adj (syndrome$ or disorder$ or disease$)).ti,ab,kf.
453	Fraser Syndrome/
454	(fraser$ adj (syndrome$ or disease$ or disorder$)).ti,ab,kf.
455	cryptophthalmos.ti,ab,kf.
456	(cyclopia$1 or cyclocephal$ or synophthalmi$).ti,ab,kf.
457	Goldenhar Syndrome/
458	(goldenhar$ or oculo-auriculo-vertebral).ti,ab,kf.
459	Mobius Syndrome/
460	((m?bius$ or moebius$) adj (syndrome$ or disease$ or disorder$)).ti,ab,kf.
461	Orofaciodigital Syndromes/
462	(orofaciodigital or oro-facial-digital or oral-facial-digital or papillon-league$ or psaume$).ti,ab,kf.
463	(robin$ adj (syndrome$ or disorder$ or disease$)).ti,ab,kf.

464	(freeman-sheldon$ or distal arthrogrypos$ or craniocarpotarsal dysplas$ or craniocarpotarsal dystroph$ or canio-carpo-tarsal or windmill-vane-hand$ or whistling-face).ti,ab,kf.
465	De Lange Syndrome/
466	((de lange$ or bushy$) adj (syndrome$ or disorder$ or disease$)).ti,ab,kf.
467	amsterdam dwarfism.ti,ab,kf.
468	(aarskog or faciodigitogenital or facio-digito-genital or facial digital genital or shawl scrotum or faciogenital or facio-genital).ti,ab,kf.
469	Cockayne Syndrome/
470	(cockayne$ or neill-dingwall$).ti,ab,kf.
471	(cerebro-oculo-facio-skeletal or cerebro-oculo-facial-skeletal).ti,ab,kf.
472	(dubowitz$ adj (syndrome$ or disease$ or disorder$)).ti,ab,kf.
473	(robinow$ or robinhow$).ti,ab,kf.
474	(f?etal face or f?etal facies or f?etal faces or acral dysostos$ or mesomelic dwarfism or covesdem$).ti,ab,kf.
475	Silver-Russell Syndrome/
476	(silver-russell$ or russell-silver$).ti,ab,kf.
477	(silver$ adj (syndrome$ or disease$ or disorder$)).ti,ab,kf.
478	((seckel$ or harper$) adj (syndrome$ or disease$ or disorder$)).ti,ab,kf.
479	(microcephalic primordial dwarfism or bird-headed dwarf$ or virchow-seckel dwarfism).ti,ab,kf.
480	Smith-Lemli-Opitz Syndrome/
481	(smith-lemli-opitz$ or dehydrocholesterol reductase deficien$).ti,ab,kf.
482	Prader-Willi Syndrome/
483	(prader-willi$ or pradar-willi$).ti,ab,kf.
484	Rubinstein-Taybi Syndrome/
485	(rubinstein-taybi$ or rubenstein-tabyii$ or broad thumb-hallux).ti,ab,kf.
486	((rubinstein$ or rubenstein$) adj2 (syndrome$ or disease$ or disorder$)).ti,ab,kf.
487	Nephritis, Hereditary/
488	(alport$ adj (syndrome$ or disease$ or disorder$)).ti,ab,kf.
489	(hereditary nephritis or h?emorrhagic familial nephritis).ti,ab,kf.
490	(hereditary deafness adj3 nephropath$).ti,ab,kf.
491	(h?ematuria adj3 nephropath$ adj3 deafness).ti,ab,kf.
492	Laurence-Moon Syndrome/
493	laurence-moon$.ti,ab,kf.
494	Bardet-Biedl Syndrome/
495	(bardet-biedl$ or biedl-bardet$).ti,ab,kf.
496	Zellweger Syndrome/
497	zellweger$.ti,ab,kf.
498	((cerebrohepatorenal or cerebro-hepato-renal) adj (syndrome$ or disease$ or disorder$)).ti,ab,kf.
499	(edward$ adj (syndrome$ or disease$ or disorder$)).ti,ab,kf.
500	"trisomy 18".ti,ab,kf.
501	(patau$ adj (syndrome$ or disease$ or disorder$)).ti,ab,kf.
502	("trisomy 13" or "trisomy D").ti,ab,kf.
503	"trisomy 22".ti,ab,kf.
504	"trisomy 9".ti,ab,kf.
505	"trisomy 10".ti,ab,kf.
506	duplication syndrome$.ti,ab,kf.
507	(("chromosome 8" or "chr 8") adj5 duplicat$).ti,ab,kf.

508	Chromosome Duplication/
509	exp X Chromosome/ab
510	exp X Chromosome/ and duplicat$.ti,ab,kf.
511	(("chromosome x" or "chr x") and duplicat$).ti,ab,kf.
512	(chromosom$ abnormality adj5 duplicat$).ti,ab,kf.
513	"tetrasomy 5p".ti,ab,kf.
514	(tetrasomy adj3 mosaic$).ti,ab,kf.
515	Chromosomes, Human, Pair 5/ and Mosaicism/
516	Tetrasomy/
517	Trisomy/ and (chromosomes, human, pair 9/ or chromosomes, human, pair 10/ or chromosomes, human, pair 13/ or Chromosomes, Human, Pair 18/ or chromosomes, human, pair 22/)
518	Chromosome Deletion/ and Chromosomes, Human, Pair 4/
519	(delet$ adj5 short arm adj5 "chrom$ 4").ti,ab,kf.
520	Wolf-Hirschhorn Syndrome/
521	((wolf-hirschhorn$ or wolff hirschorn$ or chromosome deletion dillan$ or pitt-rogers-dank$ or pitt$) adj3 (syndrome$ or disease$ or disorder$)).ti,ab,kf.
522	Cri-du-Chat Syndrome/
523	((cri du chat$ or crying cat$ or 5p or lejeune$) adj3 (syndrome$ or disease$ or disorder$)).ti,ab,kf.
524	Jacobsen Distal 11q Deletion Syndrome/
525	((jacobsen$ or 11q deletion) adj5 (syndrome$ or disease$ or disorder$)).ti,ab,kf.
526	exp Monosomy/ and Chromosomes, Human, Pair 9/
527	(9p minus or 9p deletion).ti,ab,kf.
528	(alfi$ adj (syndrome$ or disease$ or disorder$)).ti,ab,kf.
529	(degouchy$ or de gouchy$ or degrouchy$ or de grouchy$).ti,ab,kf.
530	distal 18q.ti,ab,kf.
531	Hypoventilation/cn
532	(ondine$ curse or congenital central hypoventilation or primary alveolar hypoventilation).ti,ab,kf.
533	Graft vs Host Disease/ and (Chronic Disease/ or chronic$.ti,ab,kf.)
534	(((graft vs host or graft versus host) adj (disease$ or syndrome$ or disorder)) and chronic$).ti,ab,kf.
535	or/1-534
536	Terminally Ill/
537	Terminal Care/
538	Palliative Care/
539	Hospices/ or Hospice Care/
540	(life adj2 limit$).ti,ab,kf.
541	(life adj2 threaten$).ti,ab,kf.
542	end of life.ti,ab,kf.
543	eol.ti,ab,kf.
544	(terminal$ adj2 (ill or illness$ or condition$1 or disease$1 or syndrome$ or disorder$)).ti,ab,kf.
545	(terminal adj2 (care$ or caring)).ti,ab,kf.
546	palliat$.ti,ab,kf.
547	(care adj2 dying).ti,ab,kf.
548	(technology adj2 dependent).ti,ab,kf.
549	hospice$.ti,ab,kf.
550	Rare Diseases/

551	Metabolic Diseases/
552	(severe adj2 (need or needs or illness$ or disease$1 or disabilit$ or impairment$1 or impediment$1 or condition$1 or disadvant$ or problem$1 or syndrome$1 or disorder$1)).ti,ab,kf.
553	(complex adj2 (need or needs or illness$ or disease$1 or disabilit$ or impairment$1 or impediment$1 or condition$1 or disadvant$ or problem$1 or syndrome$1 or disorder$1)).ti,ab,kf.
554	(rare adj2 (illness$ or disease$ or disabilit$ or impairment$ or impediment$ or condition$1 or syndrome$1 or disorder$1)).ti,ab,kf.
555	(multiple adj2 (need or needs or illness$ or disease$1 or disabilit$ or impairment$1 or impediment$ or condition$1 or disadvant$ or health or syndrome$1 or disorder$1)).ti,ab,kf.
556	(profound adj2 (need or needs or illness$ or disease$ or disabilit$ or impairment$ or impediment$ or condition$1 or syndrome$1 or disorder$1)).ti,ab,kf.
557	(intense adj2 (need or needs or illness$ or disease$ or disabilit$ or impairment$ or impediment$ or condition$1 or syndrome$1 or disorder$1)).ti,ab,kf.
558	(serious adj2 (disabilit$ or impairment$ or impediment$ or condition$1 or disadvant$)).ti,ab,kf.
559	or/536-558
560	exp HIV/
561	exp HIV Infections/
562	(HIV or human immunodeficiency virus$).ti,ab,kf.
563	(htlv or human t-lymphotropic virus$ or human t cell lymphotropic virus$).ti,ab,kf.
564	(acquired immune deficiency syndrome$ or acquired immunodeficiency syndrome$).ti,ab,kf.
565	(AIDS adj3 (virus$ or infection$)).ti,ab,kf.
566	(AIDS adj (related or associated)).ti,ab,kf.
567	exp Neoplasms/
568	(cancer$ or carcin$ or tumor$ or tumour$ or neoplas$ or adenocarcin$ or oncol$ or malignan$).ti,ab,kf.
569	Cystic Fibrosis/
570	(cystic fibrosis or fibrocystic or fibro-cystic or mucoviscidosis or cf).ti,ab,kf.
571	Cerebral Palsy/
572	(cerebr$ adj3 pals$).ti,ab,kf.
573	Muscle Spasticity/
574	spasticit$.ti,ab,kf.
575	Quadriplegia/
576	(spastic$ and (quadripleg$ or tetrapleg$)).ti,ab,kf.
577	exp Renal Insufficiency/
578	((kidney$ or renal) adj3 (failure$ or insufficienc$)).ti,ab,kf.
579	(end stage adj3 (kidney or renal)).ti,ab,kf.
580	(("stage 5" or "stage V") adj3 (kidney or renal)).ti,ab,kf.
581	(ESRD or ESKD or ESRF or ESKF or CRF or CKF).ti,ab,kf.
582	or/560-581
583	535 or 559 or 582
584	((Young adj1 people$) or Youth$ or Care leaver$ or residential child$ or Adolescen$ or Young adult$ or Young person$ or Young men$ or Young women$ or Teen$ or juvenile$ or Younger people or Youngster$ or Looked after or Child

	welfare or paediatric$ or pediatric$ or peadiatric$ or Young male$ or Young female$ or juvenile or children$ or child or childhood or (young adj1 patient$) or young carer$ or minors or puber$ or pubescen$ or ((secondary or high*) adj2 (school* or education))).ti,ab.
585	exp infant/
586	Child/
587	586 not 585
588	Disabled children/
589	exp Young Adult/
590	Adolescent, Hospitalized/
591	Adolescent, Institutionalized/
592	Child, Institutionalized/
593	Child, Hospitalized/
594	exp Adolescent/
595	or/584,587-594
596	((transition$ or transfer$ or handoff or handover or hand over) and (Service$ or care or clinic$ or healthcare or hospital$ or center$ or centre$ or facility or facilities or unit$ or department$ or institution$ or agency or agencies or hospice$ or provider$ or program$ or Coordinat$ or Framework$ or Managing or Managed or preparedness or Planning or Preparing or Preparation$ or Plan$ or Protocol$ or planned or Support or Supporting or Trajectory or Trajectories or Pathway$ or Process or Processes or Readiness or Partnership$ or programme$ or program$ or training or strateg$ or Failure$ or Barrier$ or system?)).ti.
597	((transition$ or transfer$ or handoff or handover or hand over) adj3 (Service$ or care or clinic$ or healthcare or hospital$ or center$ or centre$ or facility or facilities or unit$ or department$ or institution$ or agency or agencies or hospice$ or provider$ or program$ or Coordinat$ or Framework$ or Managing or Managed or preparedness or Planning or Preparing or Preparation$ or Plan$ or Protocol$ or planned or Support or Supporting or Trajectory or Trajectories or Pathway$ or Process or Processes or Readiness or Partnership$ or programme$ or program$ or training or strateg$ or Failure$ or Barrier$ or system?)).ab.
598	(continu$ and (care or healthcare or Support or Supporting or Failure$ or Barrier$)).ti.
599	(continu$ adj3 (care or healthcare or Support or Supporting or Failure$ or Barrier$)).ab.
600	transition to adult care/
601	continuity of patient care/
602	patient handoff/
603	Patient Care Planning/
604	Patient transfer/
605	(transition$ or transfer$ or handoff or handover or hand$ over).ti,ab.
606	(601 or 603) and 605
607	or/596-600,602,604,606
608	583 and 595 and 607
609	(letter or editorial or comment or news).pt.
610	exp animals/ not humans/
611	608 not (609 or 610)
612	limit 611 to (english language and yr="1990 -Current")

Embase (Ovid)

Concepts:

4. LLC: lines 1-584
5. Child/young adult: lines 585-596
6. Transition: lines 597-608

1	Creutzfeldt-Jakob disease/
2	(creutzfeldt-jakob$ or jakob-creutzfeldt$ or cjd or spongiform encephalopath$).ti,ab,kf.
3	Subacute Sclerosing Panencephalitis/
4	(subacute sclerosing panencephalit$ or sub-acute sclerosing panencephalit$ or sspe or subacute sclerosing leukoencephalit$ or sub-acute sclerosing leukoencephalit$ or van bogaert$ leukoencephalit$ or measles inclusion body encephalit$ or mibe).ti,ab,kf.
5	beta Thalassemia/
6	(beta adj (thalass?emi$ or thalas?emi$)).ti,ab,kf.
7	((thalass?emi$ or thalas?emi$) adj major).ti,ab,kf.
8	exp Aplastic Anemia/
9	((hypoplastic or aplastic) adj an?emi$).ti,ab,kf.
10	(medullary adj3 hypoplas$).ti,ab,kf.
11	exp Neutropenia/
12	((severe or chronic$) adj3 neutropeni$).ti,ab,kf.
13	immune deficiency/ or acquired immune deficiency syndrome/
14	(immun$ deficiency adj (syndrome$ or disease$ or disorder$)).ti,ab,kf.
15	(immunodeficiency adj (syndrome$ or disease$ or disorder$)).ti,ab,kf.
16	DiGeorge Syndrome/
17	(digeorge$ or di george$ or sedlackova$ or opitz g-bbb or velocardiofacial or velo-cardiofacial or velo-cardio-facial or shprintzen$ or ctaf).ti,ab,kf.
18	((deletion or vcf or pharyngeal pouch or thymic aplasia or anomaly face) adj (syndrome$ or disease$ or disorder$)).ti,ab,kf.
19	Common Variable Immunodeficiency/
20	((common variable or late onset) adj3 (immunodeficienc$ or immune deficienc$ or immunoglobulin deficienc$ or hypogammaglobulin$)).ti,ab,kf.
21	acquired hypogammaglobulin$.ti,ab,kf.
22	Cryoglobulinemia/
23	cryoglobulin?em$.ti,ab,kf.
24	Polyendocrinopathy/
25	((autoimmune or failure$) adj3 (polyglandular$ or polyendocrin$)).ti,ab,kf.
26	Progeria/
27	(progeria or hutchinson-gilford$).ti,ab,kf.
28	Tyrosinemias/
29	tyrosin?em$.ti,ab,kf.
30	Maple Syrup Urine Disease/
31	(maple syrup urine or msud).ti,ab,kf.
32	branched chain.ti,ab,kf.
33	(bckd adj5 (deficienc$ or ketoacid$ or keto-acid$)).ti,ab,kf.
34	hyperleucine-isoleucin$.ti,ab,kf.
35	Methylmalonic Acid/

36	(methylmalonic acid?emi$ or methylmalonic aciduri$ or methyl malonic acid?emi$ or methyl malonic aciduri$).ti,ab,kf.
37	Propionic Acidemia/
38	(propionic acid?em$ or propionic acidur$ or propionyl-CoA carboxylase deficienc$ or ketotic glycin?em$).ti,ab,kf.
39	Adrenoleukodystrophy/
40	(adrenoleukodystroph$ or x-ald or schilder-addison$ or addison-schilder$ or adrenomyeloneuropath$).ti,ab,kf.
41	Carnitine Palmitoyltransferase/
42	((carnitine palmityltransferase or carnitine palmitoyltransferase or carnitine o-palmityltransferase or carnitine o-palmitoyltransferase) adj3 deficienc$).ti,ab,kf.
43	Fanconi renotubular Syndrome/
44	(fanconi$ adj (syndrome$ or disease$ or disorder$)).ti,ab,kf.
45	(ocular adj3 (renal or kidney)).ti,ab,kf.
46	Cystinosis/
47	(cystinos$ or cystine storage or cystine diathes$ or cystine disease$).ti,ab,kf.
48	Lowe Syndrome/
49	((lowe or lowes or oculocerebrorenal or cerebrooculorenal or cerebro-oculo-renal) adj3 (syndrome$ or disease$ or disorder$)).ti,ab,kf.
50	Metalloprotein/ and deficien$.mp.
51	Molybdenum/ and deficien$.mp.
52	(molybdenum cofactor deficien$ or molybdenum co-factor deficien$).ti,ab,kf.
53	Oxidoreductases Acting on Sulfur Group Donors/ and Deficien$.mp.
54	Sulfite Oxidase/ and deficien$.mp.
55	((sulphite$ or sulfite$) adj3 oxidase deficien$).ti,ab,kf.
56	Argininosuccinic Acid/
57	(argininosuccinic acidur$ or argininosuccinic acid?emi$).ti,ab,kf.
58	Citrullinemia/
59	(citrullin?emi$ or citrullinuri$).ti,ab,kf.
60	"disorders of amino acid and protein metabolism"/
61	(glutaric acid?emi$ or glutaric aciduri$).ti,ab,kf.
62	Hyperglycinemia/
63	(glycine encephalopath$ or non-ketotic hyperglycin?emi$ or nonketotic hyperglycin?emi$).ti,ab,kf.
64	Hyperargininemia/
65	(arginin?emi$ or arginase deficien$ or hyperarginin?emi$).ti,ab,kf.
66	Aminoaciduria/
67	(aminoaciduri$ or aminoacid?emi$).ti,ab,kf.
68	exp glycogen storage disease/
69	(glycogen storage adj (disease$ or syndrome$ or disorder$)).ti,ab,kf.
70	(pompe$ adj (disease$ or syndrome$ or disorder$)).ti,ab,kf.
71	Galactosemia/
72	galactos?emi$.ti,ab,kf.
73	Pyruvate Dehydrogenase Complex Deficiency/
74	(pyruvate dehydrogenase adj3 deficien$).ti,ab,kf.
75	(oxalosis and (renal or kidney$)).ti,ab,kf.
76	exp Gangliosidosis/
77	gangliosidos$.ti,ab,kf.
78	(sandhoff$ adj (disease$ or syndrome$ or disorder$)).ti,ab,kf.
79	tay sach$.ti,ab,kf.

80	Mucolipidosis/
81	mucolipidos$.ti,ab,kf.
82	Canavan Disease/
83	(canavan$ leucodystroph$ or aspartoacylase deficien$ or aminoacylase 2 deficien$).ti,ab,kf.
84	((canavan$ or canavan-van bogaert-bertrand$) adj (disease$ or syndrome$ or disorder$)).ti,ab,kf.
85	Gaucher Disease/
86	(gaucher$ adj (disease$ or syndrome$ or disorder$)).ti,ab,kf.
87	(glucocerebrosidase deficien$ or glucosylceramidase deficien$).ti,ab,kf.
88	Metachromatic Leukodystrophy/
89	(metachromatic leukodystroph$ or arylsulfatase A deficien$ or metachromic leukodystroph$).ti,ab,kf.
90	exp Niemann Pick Disease/
91	(niemann-pick$ or sphingomyelinase deficien$).ti,ab,kf.
92	Sphingolipidosis/
93	sphingolipidos$.ti,ab,kf.
94	Fabry Disease/
95	(fabry$ adj (disease$ or syndrome$ or disorder$)).ti,ab,kf.
96	(angiokeratoma corporis diffusum or alpha-galactosidase A deficien$).ti,ab,kf.
97	Globoid Cell Leukodystrophy/
98	(krabbe$ adj (disease$ or syndrome$ or disorder$)).ti,ab,kf.
99	(globoid cell leukodystroph$ or galactosylceramide lipidos$ or galactosylcerebrosidase deficien$ or galactosylceramidase deficien$).ti,ab,kf.
100	Farber disease/
101	(farber$ adj (disease$ or syndrome$ or disorder$)).ti,ab,kf.
102	(farber$ lipogranulomatos$ or ceramidase deficien$ or fibrocytic dysmucopolysaccharidos$).ti,ab,kf.
103	Pelizaeus Merzbacher Disease/
104	pelizaeus-merzbacher$.ti,ab,kf.
105	Sulfatase/ and deficien$.mp.
106	Multiple Sulfatase Deficiency/
107	(sulfatase deficien$ or sulphatase deficien$ or mucosulfatidos$).ti,ab,kf.
108	(austin$ adj (disease$ or syndrome$ or disorder$)).ti,ab,kf.
109	Metachromatic Leukodystrophy/
110	sulfatidos$.ti,ab,kf.
111	histiocytosis/
112	sea-blue histiocyt$.ti,ab,kf.
113	Neuronal Ceroid-Lipofuscinosis/
114	(batten$ adj (disease$ or syndrome$ or disorder$)).ti,ab,kf.
115	(neuronal ceroid lipofuscinos$ or santavuori-haltia$ or jansky-bielschowsky$ or bielschowsky-jansky$).ti,ab,kf.
116	(kuf$ adj (disease$ or syndrome$ or disorder$)).ti,ab,kf.
117	spielmeyer vogt$.ti,ab,kf.
118	Cerebrotendinous Xanthomatosis/
119	((cerebrotendineous or cerebrotendinous or cerebrotendious or cerebral) adj3 (xanthomatos$ or cholesteros$)).ti,ab,kf.
120	bogaert-scherer-epstein$.ti,ab,kf.
121	Wolman Disease/
122	(wolman$ adj (disease$ or syndrome$ or disorder$)).ti,ab,kf.

123	lysosomal acid lipase deficien$.ti,ab,kf.
124	exp Mucopolysaccharidosis/
125	mucopolysaccharidos$.ti,ab,kf.
126	(hurler$ adj2 (syndrome$ or disease$ or disorder$)).ti,ab,kf.
127	(hunter$ adj2 (syndrome$ or disease$ or disorder$)).ti,ab,kf.
128	(MPS1 or MPS2 or MPS3 or MPS4 or MPS5 or MPS6 or MPS7 or MPS-1 or MPS-2 or MPS-3 or MPS-4 or MPS-5 or MPS-6 or MPS-7 or MPSI or MPSII or MPSIII or MPSIV or MPSV or MPSVI or MPSVII or MPS-I or MPS-II or MPS-III or MPS-IV or MPS-V or MPS-VI or MPS-VII).ti,ab,kf.
129	(beta glucuronidase deficien$ or sly syndrome$ or sly disorder$ or sly disease$).ti,ab,kf.
130	(maroteaux-lamy$ or marotaeux-lamy$ or polydystrophic dwarfism).ti,ab,kf.
131	(morquio$ or moriquio$ or beta galactosidase deficien$).ti,ab,kf.
132	(sanfilippo$ or sanfillipo$).ti,ab,kf.
133	Mucolipidosis/
134	(mucolipidos$ or pseudo-hurler$ or pseudohurler$).ti,ab,kf.
135	((inclusion-cell or i-cell) adj (disease$ or syndrome$ or disorder$)).ti,ab,kf.
136	Fucosidosis/
137	(fucosidos$ or fucidos$).ti,ab,kf.
138	Congenital Disorder of Glycosylation/
139	((cdg or ctg) adj (disease$ or disorder$ or syndrome$)).ti,ab,kf.
140	(carbohydrate-deficient glycoprotein adj (disease$ or disorder$ or syndrome$)).ti,ab,kf.
141	(congenital disorder$ adj3 glycosylation).ti,ab,kf.
142	Lesch Nyhan Syndrome/
143	((nyhan$ or kelley-seegmiller$) adj (syndrome$ or disorder$ or disease$)).ti,ab,kf.
144	juvenile gout.ti,ab,kf.
145	Menkes Syndrome/
146	menkes$.ti,ab,kf.
147	((copper transport or steely hair or kinky hair) adj (disease$ or syndrome$ or disorder$)).ti,ab,kf.
148	alpha 1 Antitrypsin Deficiency/
149	(antitrypsin deficien$ or A1AD).ti,ab,kf.
150	(AAT deficien$ or alpha-1 protease deficien$).ti,ab,kf.
151	bisalbumin?emi$.ti,ab,kf.
152	Congenital Generalized Lipodystrophy/
153	(congenital generali?ed lipodystroph$ or berardinelli$ or bernardnelli$).ti,ab,kf.
154	Landau Kleffner Syndrome/
155	(landau-kleffner$ or infantile acquired aphasia$ or acquired epileptic aphasia$).ti,ab,kf.
156	(aphasia$ adj5 convulsive).ti,ab,kf.
157	Rett Syndrome/
158	(rett$ adj (syndrome$ or disease$ or disorder$)).ti,ab,kf.
159	cerebroatrophic hyperammon?emi$.ti,ab,kf.
160	Huntington chorea/
161	huntington$.ti,ab,kf.
162	exp spinocerebellar degeneration/
163	((nyhan$ or kelley-seegmiller$) adj (syndrome$ or disorder$ or disease$)).ti,ab,kf.
164	(spinocerebellar ataxia$ or ataxia$ telangiectasia$ or louis-bar$ syndrome$ or louis-bar$ disease$ or louis-bar$ disorder$ or machado-joseph$ or joseph$ disease$ or joseph$ disorder$ or joseph$ syndrome$).ti,ab,kf.
165	Friedreich Ataxia/
166	((friedreich$ or friedrich$) adj3 ataxia$).ti,ab,kf.

167	spinocerebellar degenerat$.ti,ab,kf.
168	hereditary spinal muscular atrophy/
169	(spinal muscular atroph$ or werdnig hoffman$).ti,ab,kf.
170	(dubowitz$ or kugelberg-welander$).ti,ab,kf.
171	Bulbar paralysis/
172	(fazio-londe$ or faziolonde$ or progressive bulbar pals$).ti,ab,kf.
173	parkinson disease/
174	(parkinson$ or hypokinetic rigid syndrome$ or hypokinetic rigid disease$ or hypokinetic rigid disorder$ or paralysis agitan$ or shaking pals$).ti,ab,kf.
175	neurodegeneration with brain iron accumulation/
176	(pantothenate kinase-associated neurodegenerat$ or PKAN or hallervorden-spatz$).ti,ab,kf.
177	((neurodegeneration adj3 brain iron accumulation) or NBIA$1).ti,ab,kf.
178	olivopontocerebellar atrophy/
179	(olivopontocerebellar atroph$ or OPCA or olivopontocerebellar degenerat$).ti,ab,kf.
180	(multiple system atrophy adj5 cerebellar).ti,ab,kf.
181	Schilder disease/
182	(alper$ adj (disease$ or syndrome$ or disorder$)).ti,ab,kf.
183	(progressive sclerosing poliodystroph$ or progressive infantile poliodystroph$).ti,ab,kf.
184	(diffuse cerebral sclerosis adj5 schilder$).ti,ab,kf.
185	Leigh Disease/
186	(leigh$ adj (syndrome$ or disease$ or disorder$)).ti,ab,kf.
187	(subacute necrotizing encephalomyelopath$ or subacute necrotising encephalomyelopath$ or sub-acute necrotizing encephalomyelopath$ or sub-acute necrotising encephalomyelopath$ or SNEM).ti,ab,kf.
188	(aicardi-gouti?res or aicardia-gouti?res).ti,ab,kf.
189	(worster-drought$ or congenital suprabulbar pares$).ti,ab,kf.
190	multiple sclerosis/
191	(multiple sclerosis or disseminated sclerosis or encephalomyelitis disseminata$).ti,ab,kf.
192	(demyelinating adj (disease$ or syndrome$ or disorder$)).ti,ab,kf.
193	exp myoclonus epilepsy/
194	myoclonic epileps$.ti,ab,kf.
195	((lafora$ or merrf$ or unverricht-lundborg$ or janz$) adj (disease$ or syndrome$ or disorder$)).ti,ab,kf.
196	lennox-gastaut$.ti,ab,kf.
197	(lennox$ adj (syndrome$ or disease$ or disorder$)).ti,ab,kf.
198	infantile spasm/
199	(west$ adj (syndrome$ or disease$ or disorder$)).ti,ab,kf.
200	epileptic state/
201	(epilepsia partialis continua or kojevnikov$ or epilepsia partialis continuoa or kozhevnikof$).ti,ab,kf.
202	hereditary motor sensory neuropathy/
203	(charcot-marie-tooth$ or peroneal muscular atroph$).ti,ab,kf.
204	(progressive neuropathic muscular atroph$ or hereditary peroneal nerve dysfunction$ or peroneal neuropath$).ti,ab,kf.
205	hereditary motor sensory neuropathy/
206	(hereditary sensory adj3 motor neuropath$).ti,ab,kf.
207	(hereditary motor adj3 sensory neuropath$).ti,ab,kf.
208	infantile Refsum disease/
209	disorders of peroxisomal functions/

210	(infantile refsum or infantile phytanic acid storage).ti,ab,kf.
211	congenital myasthenic syndrome/
212	congenital myasth?eni$.ti,ab,kf.
213	Duchenne muscular dystrophy/
214	(duchenne muscular dystroph$ or dmd).ti,ab,kf.
215	exp limb girdle muscular dystrophy/
216	(limb-girdle or erb$ muscular dystroph$).ti,ab,kf.
217	(sarcoglycanopath$ or sarcoglycaopath$).ti,ab,kf.
218	chondrodysplasia/
219	(osteochondrodysplas$ or schwartz-jampel or chondrodystrophi$ myotoni$ or myotoni$ chondrodystrophi$).ti,ab,kf.
220	Thomsen disease/
221	(congenita$ myotoni$ or myotoni$ congenita$).ti,ab,kf.
222	(thomsen$ adj (disease$ or disorder$ or syndrome$)).ti,ab,kf.
223	((recessive adj3 myotoni$) or becker$ myotoni$).ti,ab,kf.
224	myokymia/
225	(isaac$ adj (syndrome$ or disease$ or disorder$)).ti,ab,kf.
226	neuromyotoni$.ti,ab,kf.
227	myotonia/
228	(paramyotoni$ congenita$ or congenita$ paramyotoni$).ti,ab,kf.
229	(eulenburg$ adj (disease$ or syndrome$ or disorder$)).ti,ab,kf.
230	(myotoni$ adj (disease$ or disorder$ or syndrome$)).ti,ab,kf.
231	pseudomyotoni$.ti,ab,kf.
232	exp myopathy/ and congen$.mp.
233	(congenital adj3 myopath$).ti,ab,kf.
234	myopathycongenital.ti,ab,kf.
235	((nemaline or rod) adj3 myopath$).ti,ab,kf.
236	((central core or mini-core or minicore or multicore or multi-core) adj (disease$ or disorder$ or syndrome$ or myopath$)).ti,ab,kf.
237	fiber type disproportion.ti,ab,kf.
238	fibre type disproportion.ti,ab,kf.
239	Muscular Dystrophies/cn [Congenital]
240	(congenital$ adj5 muscular dystroph$).ti,ab,kf.
241	((centronuclear or myotubular) adj myopath$).ti,ab,kf.
242	exp mitochondrial myopathy/
243	(mitochondrial myopath$ or mitochondrial encephalomyopath$ or chronic progressive external ophthalmopleg$).ti,ab,kf.
244	((melas or kearns-sayre$) adj (syndrome$ or disease$ or disorder$)).ti,ab,kf.
245	Quadriplegia/ and spastic$.ti,ab,kf.
246	(spastic quadriplegi$ or spastic tetraplegi$).ti,ab,kf.
247	Reye Syndrome/
248	(reye$ adj (syndrome$ or disease$ or disorder$)).ti,ab,kf.
249	multiple pterygium.ti,ab,kf.
250	pulmonary hypertension/ and primary$.ti,ab,kf.
251	((primary pulmonary or precapillary pulmonary or idiopathic pulmonary) adj (hypertension or ht or arterial hypertension)).ti,ab,kf.
252	((primary bronchopulmonary or precapillary bronchopulmonary or idiopathic bronchopulmonary) adj (hypertension or ht or arterial hypertension)).ti,ab,kf.
253	((primary lung or precapillary lung or idiopathic lung) adj (hypertension or ht or arterial hypertension)).ti,ab,kf.

254	ipah.ti,ab,kf.
255	congestive cardiomyopathy/
256	((congestive or dilated) adj cardiomyopath$).ti,ab,kf.
257	exp hypertrophic cardiomyopathy/
258	(hypertrophic adj cardiomyopath$).ti,ab,kf.
259	Cardiomyopathies/cn [Congenital]
260	(congenital adj3 cardiomyopath$).ti,ab,kf.
261	restrictive cardiomyopathy/
262	(restrictive cardiomyopath$ or obliterative cardiomyopath$ or constrictive cardiomyopath$).ti,ab,kf.
263	exp lung fibrosis/
264	(pulmonary fibros$ or lung fibros$ or bronchopulmonary fibros$ or fibrosing alveolit$ or interstitial pneumonit$).ti,ab,kf.
265	respiratory failure/
266	(respiratory adj (failure$ or insufficienc$)).ti,ab,kf.
267	cystic adenomatoid malformation/
268	((cystic lung or cystic pulmonary or cystic bronchopulmonary) adj (disease$ or disorder or syndrome$)).ti,ab,kf.
269	(bronchogenic cyst$ or bronchopulmonary foregut malformation$).ti,ab,kf.
270	cystic adenomatoid malformation$.ti,ab,kf.
271	lobar emphysem$.ti,ab,kf.
272	(pulmonary sequestration$ or bronchopulmonary sequestration$ or lung sequestration$ or extralobar sequestration$ or extra-lobar sequestration$ or intralobar sequestration$ or intra-lobar sequestration$).ti,ab,kf.
273	pulmolithias$.ti,ab,kf.
274	exp Liver Failure/
275	((liver$1 or hepatic) adj3 fail$).ti,ab,kf.
276	exp Liver Cirrhosis/
277	(cirrhosis adj3 liver$1).ti,ab,kf.
278	liver vein obstruction/
279	((veno-occlusive or venous occlusive) adj (disease$ or syndrome$ or disorder$)).ti,ab,kf.
280	Exocrine Pancreatic Insufficiency/
281	(swachman-diamond or shwachman-bodian or schwachmann-diamond or shwachmann-bodian).ti,ab,kf.
282	Wegener Granulomatosis/
283	wegener$ granulomatos$.ti,ab,kf.
284	(granulomatos$ adj3 polyangiit$).ti,ab,kf.
285	Osteolysis/ and essential.mp.
286	essential osteolys$.ti,ab,kf.
287	((gorham$ or gorham-stout$ or vanishing bone or phantom bone) adj (disease$ or syndrome$ or disorder)).ti,ab,kf.
288	((arc or arthrogryposis renal dysfunction cholestasis) adj (disease$ or syndrome$ or disorder)).ti,ab,kf.
289	brain hemorrhage/ and Congen$.mp.
290	brain hemorrhage/ and Traum$.mp.
291	brain hemorrhage/ and Birth Injury/
292	(cerebral h?emorrhage$ and (birth$ adj3 injur$)).ti,ab,kf.
293	newborn hypoxia/
294	asphyxia neonatorum.ti,ab,kf.
295	((perinatal$ or neonatal$ or birth$) adj3 asphyxia$).ti,ab,kf.

296	congenital rubella syndrome/
297	congenital rubella.ti,ab,kf.
298	exp Cytomegalovirus Infection/ and congen$.mp.
299	(congenital adj (cytomegalovirus$ or cmv)).ti,ab,kf.
300	(Chickenpox and Congen$).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]
301	exp Herpes Zoster/ and Congen$.mp.
302	Herpesvirus 3, Human/ and congenital$.ti,ab,kf.
303	((congenital or fetal or foetal) adj3 (varicella$ or chicken pox$ or VZV)).ti,ab,kf.
304	congenital toxoplasmosis/
305	congenital toxoplasmos$.ti,ab,kf.
306	exp brain hypoxia/
307	((brain$ or cerebral) adj3 hypoxi$).ti,ab,kf.
308	kidney failure/ and Congen$.mp.
309	acute kidney failure/ and Congen$.mp.
310	chronic kidney failure/ and Congen$.mp.
311	chronic kidney failure/ and Congen$.mp.
312	(congenital$ adj3 (kidney failure$ or renal failure$ or kidney insufficienc$ or renal insufficienc$)).ti,ab,kf.
313	(congenital$ adj3 (kidney disease$ or renal disease$)).ti,ab,kf.
314	anencephalus/
315	(anencephal$ or meroanencephal$ or craniorachischis$).ti,ab,kf.
316	(aprosencephal$ adj3 open cranium).ti,ab,kf.
317	Encephalocele/
318	(encephalocele$ or cranium bifidum).ti,ab,kf.
319	Dandy Walker Syndrome/
320	dandy-walker$.ti,ab,kf.
321	Acrocallosal Syndrome/
322	(acrocallosal or acro-callosal or acrocolossal or acro colossal).ti,ab,kf.
323	Aicardi Syndrome/
324	(aicardi$ adj (syndrome$ or disease$ or disorder$)).ti,ab,kf.
325	Holoprosencephaly/
326	(holoprosencephal$ or arhinencephal$ or holosprosencephal$).ti,ab,kf.
327	Hydranencephaly/
328	(hydranencephal$ or hydrancephal$ or hydroanencephal$).ti,ab,kf.
329	exp agyria/
330	Microcephaly/
331	(lissencephal$ or walker-warburg$ or miller-dieker$ or norman-robert$ or microlissencephal$).ti,ab,kf.
332	((fukuyama$ or muscle-eye-brain) adj (syndrome$ or disease$ or disorder$)).ti,ab,kf.
333	cortical dysplasia/
334	(microgyria$ or microgyrus or micro-gyria$ or micro-gyrus).ti,ab,kf.
335	(pachygyria$ or pachgyria$).ti,ab,kf.
336	agyria$.ti,ab,kf.
337	Septooptic Dysplasia/
338	((septo-optic or septooptic) adj dysplas$).ti,ab,kf.
339	de morsier$.ti,ab,kf.
340	(schizencephal$ or schizzencephal$).ti,ab,kf.
341	Arnold Chiari Malformation/

342	chiari$ malformation$.ti,ab,kf.
343	Persistent Truncus Arteriosus/
344	(truncus or common arterial trunk$).ti,ab,kf.
345	great vessels transposition/
346	((transposition$ or dextrotransposition$ or dtransposition$ or levotransposition$ or ltransposition$) adj3 (great arter$ or main arter$ or aorta$ or pulmonary arter$ or great vessel$ or main vessel$)).ti,ab,kf.
347	(dextro-tga or d-tga or levo-tga or l-tga).ti,ab,kf.
348	(double inlet adj3 ventricle$).ti,ab,kf.
349	DILV.ti,ab,kf.
350	single ventricle$.ti,ab,kf.
351	congenital heart malformation/ and heart atrium appendage/
352	(isomerism adj3 atrial appendage$).ti,ab,kf.
353	(aspleni$ or polyspleni$ or poly-spleni$).ti,ab,kf.
354	Fallot tetralogy/
355	(tetralogy adj3 fallot$).ti,ab,kf.
356	Eisenmenger Complex/
357	(eisenmenger$ or tardive cyanos$ or eisenmeyer$).ti,ab,kf.
358	(pentalogy adj3 fallot$).ti,ab,kf.
359	pulmonary valve atresia/
360	((pulmonary or bronchopulmonary or lung$) adj3 atresia$).ti,ab,kf.
361	tricuspid valve atresia/
362	((tricuspid or tri) adj3 atresia$).ti,ab,kf.
363	Ebstein Anomaly/
364	(ebstein$ adj (anomal$ or malformation$)).ti,ab,kf.
365	Hypoplastic Left Heart Syndrome/
366	(hypoplastic left heart adj (syndrome$ or disease$ or disorder$)).ti,ab,kf.
367	((aortic or aorta$) adj3 atresia$).ti,ab,kf.
368	(mitral adj3 atresia$).ti,ab,kf.
369	((absence$ or absent$) adj3 (aorta$ or aortic)).ti,ab,kf.
370	(aplas$ adj3 (aorta$ or aortic)).ti,ab,kf.
371	exp Aortic Aneurysm/cn [Congenital]
372	(((aorta$ or aortic) adj3 aneurys$) and congenital$).ti,ab,kf.
373	(hypoplas$ adj3 (aorta$ or aortic)).ti,ab,kf.
374	(convulsion$ adj3 (aorta$ or aortic)).ti,ab,kf.
375	(persistent right adj3 (aorta$ or aortic)).ti,ab,kf.
376	((anomalous pulmonary venous or anamolous pulmonary venous) adj (connection or drainage or return)).ti,ab,kf.
377	((absence$ or absent$) adj3 vena$ cava$).ti,ab,kf.
378	(persistent left adj3 cardinal vein$).ti,ab,kf.
379	Scimitar Syndrome/
380	((scimitar$ or pulmonary venolobar) adj (syndrome$ or disease$ or disorder$)).ti,ab,kf.
381	(arteriovenous malformations/ or intracranial arteriovenous malformations/) and bilateral.ti,ab,kf.
382	((bilateral AV or bilateral arteriovenous or bilateral arterio-venous) adj3 malform$).ti,ab,kf.
383	((trachea$ or windpipe$ or wind-pipe$) adj3 atresia$).ti,ab,kf.
384	Tracheal Stenosis/
385	((trachea$ or laryngotrachea$ or glottic or subglottic or sub-glottic) adj3 stenosis).ti,ab,kf.

386	lung dysplasia/
387	((lung$ or pulmonary or bronchopulmonary) adj3 (hypoplas$ or dysplas$)).ti,ab,kf.
388	((absence$ or absent$) adj3 (esophag$ or oesophag$ or foodpipe or food-pipe$ or gullet$)).ti,ab,kf.
389	intestine atresia/
390	(duoden$ adj3 atresia$).ti,ab,kf.
391	((absence$ or absent$) adj3 (intestin$ or gastrointestin$)).ti,ab,kf.
392	((intestin$ or gastrointestin$) adj3 atresia$).ti,ab,kf.
393	((intestin$ or gastrointestin$) adj3 stenos$).ti,ab,kf.
394	(cloaca$ adj3 (abnor$ or malform$ or anomal$)).ti,ab,kf.
395	(cloaca$ adj3 exopthalmo$).ti,ab,kf.
396	bile duct atresia/
397	(biliary adj3 atresia$).ti,ab,kf.
398	(extrahepatic ductopen$ or extra-hepatic ductopen$ or progressive obliterative cholangiopath$).ti,ab,kf.
399	(biliary adj3 hypoplas$).ti,ab,kf.
400	(alagille$ adj3 atresia$).ti,ab,kf.
401	((absence$ or absent$) adj3 kidney$).ti,ab,kf.
402	(potter$ adj (sequence$ or syndrome$ or disease$ or disorder$)).ti,ab,kf.
403	Oligohydramnios/
404	oligohydramn$.ti,ab,kf.
405	Multicystic Dysplastic Kidney/
406	((kidney$ or renal) adj3 dysplas$).ti,ab,kf.
407	((meckel$ or meckelgruber$ or gruber$) adj (syndrome$ or disease$ or disorder$)).ti,ab,kf.
408	dysencephalia splanchnocystica$.ti,ab,kf.
409	(pena-shokeir$ or penn-shokeir$).ti,ab,kf.
410	(larsen$ adj (syndrome$ or disease$ or disorder$)).ti,ab,kf.
411	acrocephalosyndactyly/
412	acrocephalosyndactyl$.ti,ab,kf.
413	(pfeiffer$ adj (syndrome$ or disease$ or syndrome$)).ti,ab,kf.
414	chondrodysplasia/
415	short rib$1.ti,ab,kf.
416	(saldino-noonan$ or majewski$ or verma-naumoff$ or beemer-langer$).ti,ab,kf.
417	(jeune$ adj (syndrome$ or disease$ or disorder$)).ti,ab,kf.
418	asphyxiating thoracic dysplas$.ti,ab,kf.
419	exp chondrodysplasia punctata/
420	chondrodysplasia punctata$.ti,ab,kf.
421	((conradi$ or h?nermann$ or happle$) adj3 (syndrome$ or disease$ or disorder$)).ti,ab,kf.
422	Osteogenesis Imperfecta/
423	osteogenesis imperfecta.ti,ab,kf.
424	((brittle bone or lobstein$) adj (disease$ or disorder$ or syndrome$)).ti,ab,kf.
425	chondrodysplasia/
426	(spondyloepimetaphyseal or spondyloepiphyseal or spendylo metaphyseal).ti,ab,kf.
427	umbilical hernia/
428	(omphalocele$ or omphalocoele$ or exomphalos).ti,ab,kf.
429	(hernia$ adj3 umbilic$).ti,ab,kf.
430	Gastroschisis/
431	gastroschis$.ti,ab,kf.

432	lamellar ichthyosis/
433	(lamellar$ adj3 ichthyos$).ti,ab,kf.
434	((harlequin$ or harloquin$) adj3 (ichthyos$ or baby or babies or f?etus$)).ti,ab,kf.
435	(ichthyosis congenita$ or ichthyosis fetalis or keratosis diffusa fetalis).ti,ab,kf.
436	exp Epidermolysis Bullosa/
437	epidermolysis bullosa$.ti,ab,kf.
438	(johanson-blizzard$ or johanna-blizzard$).ti,ab,kf.
439	Xeroderma Pigmentosum/
440	xeroderma pigmentosum.ti,ab,kf.
441	Ectodermal Dysplasia/
442	lacrimo-auriculo-dento-digital.ti,ab,kf.
443	ectodermal dysplas$.ti,ab,kf.
444	((ladd or eec) adj (syndrome$ or disease$ or disorder$)).ti,ab,kf.
445	Sturge Weber Syndrome/
446	(sturge-weber or encephalotrigeminal angiomatos$).ti,ab,kf.
447	fetal alcohol syndrome/
448	f?etal alcohol.ti,ab,kf.
449	Pierre Robin Syndrome/
450	pierre robin$.ti,ab,kf.
451	acrocephalosyndactyly/
452	(acrocephalosyndact$ or acrocephalopolysyndact$).ti,ab,kf.
453	((apert$ or crouzon$ or saethre-chotzen$ or noack$ or carpenter$ or sakati-nyhan-tisdale$ or goodman$) adj (syndrome$ or disorder$ or disease$)).ti,ab,kf.
454	Fraser Syndrome/
455	(fraser$ adj (syndrome$ or disease$ or disorder$)).ti,ab,kf.
456	cryptophthalmos.ti,ab,kf.
457	(cyclopia$1 or cyclocephal$ or synophthalmi$).ti,ab,kf.
458	Goldenhar Syndrome/
459	(goldenhar$ or oculo-auriculo-vertebral).ti,ab,kf.
460	Mobius Syndrome/
461	((m?bius$ or moebius$) adj (syndrome$ or disease$ or disorder$)).ti,ab,kf.
462	dysostosis/
463	(orofaciodigital or oro-facial-digital or oral-facial-digital or papillon-league$ or psaume$).ti,ab,kf.
464	(robin$ adj (syndrome$ or disorder$ or disease$)).ti,ab,kf.
465	(freeman-sheldon$ or distal arthrogrypos$ or craniocarpotarsal dysplas$ or craniocarpotarsal dystroph$ or canio-carpo-tarsal or windmill-vane-hand$ or whistling-face).ti,ab,kf.
466	De Lange Syndrome/
467	((de lange$ or bushy$) adj (syndrome$ or disorder$ or disease$)).ti,ab,kf.
468	amsterdam dwarfism.ti,ab,kf.
469	(aarskog or faciodigitogenital or facio-digito-genital or facial digital genital or shawl scrotum or faciogenital or facio-genital).ti,ab,kf.
470	Cockayne Syndrome/
471	(cockayne$ or neill-dingwall$).ti,ab,kf.
472	(cerebro-oculo-facio-skeletal or cerebro-oculo-facial-skeletal).ti,ab,kf.
473	(dubowitz$ adj (syndrome$ or disease$ or disorder$)).ti,ab,kf.
474	(robinow$ or robinhow$).ti,ab,kf.
475	(f?etal face or f?etal facies or f?etal faces or acral dysostos$ or mesomelic dwarfism or covesdem$).ti,ab,kf.

476	Silver Russell Syndrome/
477	(silver-russell$ or russell-silver$).ti,ab,kf.
478	(silver$ adj (syndrome$ or disease$ or disorder$)).ti,ab,kf.
479	((seckel$ or harper$) adj (syndrome$ or disease$ or disorder$)).ti,ab,kf.
480	(microcephalic primordial dwarfism or bird-headed dwarf$ or virchow-seckel dwarfism).ti,ab,kf.
481	Smith Lemli Opitz Syndrome/
482	(smith-lemli-opitz$ or dehydrocholesterol reductase deficien$).ti,ab,kf.
483	Prader Willi Syndrome/
484	(prader-willi$ or pradar-willi$).ti,ab,kf.
485	Rubinstein syndrome/
486	(rubinstein-taybi$ or rubenstein-tabyii$ or broad thumb-hallux).ti,ab,kf.
487	((rubinstein$ or rubenstein$) adj2 (syndrome$ or disease$ or disorder$)).ti,ab,kf.
488	nephritis/ and (hered$ or inherit$).mp.
489	(alport$ adj (syndrome$ or disease$ or disorder$)).ti,ab,kf.
490	(hereditary nephritis or h?emorrhagic familial nephritis).ti,ab,kf.
491	(hereditary deafness adj3 nephropath$).ti,ab,kf.
492	(h?ematuria adj3 nephropath$ adj3 deafness).ti,ab,kf.
493	Laurence Moon Syndrome/
494	laurence-moon$.ti,ab,kf.
495	Bardet Biedl Syndrome/
496	(bardet-biedl$ or biedl-bardet$).ti,ab,kf.
497	Zellweger Syndrome/
498	zellweger$.ti,ab,kf.
499	((cerebrohepatorenal or cerebro-hepato-renal) adj (syndrome$ or disease$ or disorder$)).ti,ab,kf.
500	(edward$ adj (syndrome$ or disease$ or disorder$)).ti,ab,kf.
501	"trisomy 18".ti,ab,kf.
502	(patau$ adj (syndrome$ or disease$ or disorder$)).ti,ab,kf.
503	("trisomy 13" or "trisomy D").ti,ab,kf.
504	"trisomy 22".ti,ab,kf.
505	"trisomy 9".ti,ab,kf.
506	"trisomy 10".ti,ab,kf.
507	duplication syndrome$.ti,ab,kf.
508	(("chromosome 8" or "chr 8") adj5 duplicat$).ti,ab,kf.
509	Chromosome Duplication/
510	exp X Chromosome/ and abnorm$.mp.
511	exp X Chromosome/ and duplicat$.ti,ab,kf.
512	(("chromosome x" or "chr x") and duplicat$).ti,ab,kf.
513	(chromosom$ abnormality adj5 duplicat$).ti,ab,kf.
514	"tetrasomy 5p".ti,ab,kf.
515	(tetrasomy adj3 mosaic$).ti,ab,kf.
516	Chromosome 5/ and Mosaicism/
517	Tetrasomy/
518	Trisomy/ and (chromosome 9/ or chromosome 10/ or chromosome 13/ or Chromosome 18/ or chromosome 22/)
519	Chromosome Deletion/ and Chromosome 4/
520	(delet$ adj5 short arm adj5 "chrom$ 4").ti,ab,kf.
521	Wolf Hirschhorn Syndrome/

522	((wolf-hirschhorn$ or wolff hirschorn$ or chromosome deletion dillan$ or pitt-rogers-dank$ or pitt$) adj3 (syndrome$ or disease$ or disorder$)).ti,ab,kf.
523	cat cry Syndrome/
524	((cri du chat$ or crying cat$ or 5p or lejeune$) adj3 (syndrome$ or disease$ or disorder$)).ti,ab,kf.
525	Jacobsen syndrome/
526	((jacobsen$ or 11q deletion) adj5 (syndrome$ or disease$ or disorder$)).ti,ab,kf.
527	exp Monosomy/ and Chromosome 9/
528	(9p minus or 9p deletion).ti,ab,kf.
529	(alfi$ adj (syndrome$ or disease$ or disorder$)).ti,ab,kf.
530	(degouchy$ or de gouchy$ or degrouchy$ or de grouchy$).ti,ab,kf.
531	distal 18q.ti,ab,kf.
532	congenital central hypoventilation syndrome/
533	(ondine$ curse or congenital central hypoventilation or primary alveolar hypoventilation).ti,ab,kf.
534	Graft versus host reaction/ and (Chronic Disease/ or chronic$.ti,ab,kf.)
535	(((graft vs host or graft versus host) adj (disease$ or syndrome$ or disorder)) and chronic$).ti,ab,kf.
536	or/1-534
537	terminally ill patient/
538	Terminal Care/
539	palliative therapy/
540	Hospice/ or Hospice Care/
541	(life adj2 limit$).ti,ab,kf.
542	(life adj2 threaten$).ti,ab,kf.
543	end of life.ti,ab,kf.
544	eol.ti,ab,kf.
545	(terminal$ adj2 (ill or illness$ or condition$1 or disease$1 or syndrome$ or disorder$)).ti,ab,kf.
546	(terminal adj2 (care$ or caring)).ti,ab,kf.
547	palliat$.ti,ab,kf.
548	(care adj2 dying).ti,ab,kf.
549	(technology adj2 dependent).ti,ab,kf.
550	hospice$.ti,ab,kf.
551	Rare Disease/
552	metabolic disorder/
553	(severe adj2 (need or needs or illness$ or disease$1 or disabilit$ or impairment$1 or impediment$1 or condition$1 or disadvant$ or problem$1 or syndrome$1 or disorder$1)).ti,ab,kf.
554	(complex adj2 (need or needs or illness$ or disease$1 or disabilit$ or impairment$1 or impediment$1 or condition$1 or disadvant$ or problem$1 or syndrome$1 or disorder$1)).ti,ab,kf.
555	(rare adj2 (illness$ or disease$ or disabilit$ or impairment$ or impediment$ or condition$1 or syndrome$1 or disorder$1)).ti,ab,kf.
556	(multiple adj2 (need or needs or illness$ or disease$1 or disabilit$ or impairment$1 or impediment$ or condition$1 or disadvant$ or health or syndrome$1 or disorder$1)).ti,ab,kf.
557	(profound adj2 (need or needs or illness$ or disease$ or disabilit$ or impairment$ or impediment$ or condition$1 or syndrome$1 or disorder$1)).ti,ab,kf.

558	(intense adj2 (need or needs or illness$ or disease$ or disabilit$ or impairment$ or impediment$ or condition$1 or syndrome$1 or disorder$1)).ti,ab,kf.
559	(serious adj2 (disabilit$ or impairment$ or impediment$ or condition$1 or disadvant$)).ti,ab,kf.
560	or/537-559
561	exp Human immunodeficiency virus/
562	exp Human immunodeficiency virus infection/
563	(HIV or human immunodeficiency virus$).ti,ab,kf.
564	(htlv or human t-lymphotropic virus$ or human t cell lymphotropic virus$).ti,ab,kf.
565	(acquired immune deficiency syndrome$ or acquired immunodeficiency syndrome$).ti,ab,kf.
566	(AIDS adj3 (virus$ or infection$)).ti,ab,kf.
567	(AIDS adj (related or associated)).ti,ab,kf.
568	exp Neoplasm/
569	(cancer$ or carcin$ or tumor$ or tumour$ or neoplas$ or adenocarcin$ or oncol$ or malignan$).ti,ab,kf.
570	Cystic Fibrosis/
571	(cystic fibrosis or fibrocystic or fibro-cystic or mucoviscidosis or cf).ti,ab,kf.
572	Cerebral Palsy/
573	(cerebr$ adj3 pals$).ti,ab,kf.
574	spasticity/
575	spasticit$.ti,ab,kf.
576	Quadriplegia/
577	(spastic$ and (quadripleg$ or tetrapleg$)).ti,ab,kf.
578	exp kidney failure/
579	((kidney$ or renal) adj3 (failure$ or insufficienc$)).ti,ab,kf.
580	(end stage adj3 (kidney or renal)).ti,ab,kf.
581	(("stage 5" or "stage V") adj3 (kidney or renal)).ti,ab,kf.
582	(ESRD or ESKD or ESRF or ESKF or CRF or CKF).ti,ab,kf.
583	or/561-582
584	536 or 560 or 583
585	((Young adj1 people$) or Youth$ or Care leaver$ or residential child$ or Adolescen$ or Young adult$ or Young person$ or Young men$ or Young women$ or Teen$ or juvenile$ or Younger people or Youngster$ or Looked after or Child welfare or paediatric$ or pediatric$ or peadiatric$ or Young male$ or Young female$ or juvenile or children$ or child or childhood or (young adj1 patient$) or young carer$ or minors or puber$ or pubescen$ or ((secondary or high*) adj2 (school* or education))).ti,ab.
586	exp infant/
587	Child/
588	587 not 586
589	handicapped child/
590	exp Young Adult/
591	hospitalized adolescent/
592	institutionalized adolescent/
593	institutionalized child/
594	hospitalized child/
595	exp Adolescent/
596	or/585,588-595
597	((transition$ or transfer$ or handoff or handover or hand over) and (Service$ or care or clinic$ or healthcare or hospital$ or center$ or centre$ or facility or facilities or unit$ or

	department$ or institution$ or agency or agencies or hospice$ or provider$ or program$ or Coordinat$ or Framework$ or Managing or Managed or preparedness or Planning or Preparing or Preparation$ or Plan$ or Protocol$ or planned or Support or Supporting or Trajectory or Trajectories or Pathway$ or Process or Processes or Readiness or Partnership$ or programme$ or program$ or training or strateg$ or Failure$ or Barrier$ or system?)).ti.
598	((transition$ or transfer$ or handoff or handover or hand over) adj3 (Service$ or care or clinic$ or healthcare or hospital$ or center$ or centre$ or facility or facilities or unit$ or department$ or institution$ or agency or agencies or hospice$ or provider$ or program$ or Coordinat$ or Framework$ or Managing or Managed or preparedness or Planning or Preparing or Preparation$ or Plan$ or Protocol$ or planned or Support or Supporting or Trajectory or Trajectories or Pathway$ or Process or Processes or Readiness or Partnership$ or programme$ or program$ or training or strateg$ or Failure$ or Barrier$ or system?)).ab.
599	(continu$ and (care or healthcare or Support or Supporting or Failure$ or Barrier$)).ti.
600	(continu$ adj3 (care or healthcare or Support or Supporting or Failure$ or Barrier$)).ab.
601	transition to adult care/
602	patient care/
603	clinical handover/
604	Patient Care Planning/
605	patient transport/
606	(transition$ or transfer$ or handoff or handover or hand$ over).ti,ab.
607	(602 or 604) and 606
608	or/597-601,605,607
609	584 and 596 and 608
610	(letter or editorial or comment or news).pt.
611	exp animal/ not human/
612	609 not (610 or 611)
613	limit 612 to (english language and yr="1990 -Current")

Psychinfo (Ovid)

Concepts:

1. LLC: lines 1-401
2. Child/young adult: lines 402-404
3. Transition: lines 405-415

1	Creutzfeldt Jakob Syndrome/
2	(creutzfeldt-jakob$ or jakob-creutzfeldt$ or cjd or spongiform encephalopath$).ti,ab,kf.
3	(subacute sclerosing panencephalit$ or sub-acute sclerosing panencephalit$ or sspe or subacute sclerosing leukoencephalit$ or sub-acute sclerosing leukoencephalit$ or van bogaert$ leukoencephalit$ or measles inclusion body encephalit$ or mibe).ti,ab,kf.
4	(beta adj (thalass?emi$ or thalas?emi$)).ti,ab,kf.
5	((thalass?emi$ or thalas?emi$) adj major).ti,ab,kf.
6	((hypoplastic or aplastic) adj an?emi$).ti,ab,kf.
7	(medullary adj3 hypoplas$).ti,ab,kf.
8	((severe or chronic$) adj3 neutropeni$).ti,ab,kf.
9	immunologic deficiency syndromes/ or acquired immunodeficiency syndrome/
10	(immun$ deficiency adj (syndrome$ or disease$ or disorder$)).ti,ab,kf.
11	(immunodeficiency adj (syndrome$ or disease$ or disorder$)).ti,ab,kf.
12	(digeorge$ or di george$ or sedlackova$ or opitz g-bbb or velocardiofacial or velo-cardiofacial or velo-cardio-facial or shprintzen$ or ctaf).ti,ab,kf.
13	((deletion or vcf or pharyngeal pouch or thymic aplasia or anomaly face) adj (syndrome$ or disease$ or disorder$)).ti,ab,kf.
14	((common variable or late onset) adj3 (immunodeficienc$ or immune deficienc$ or immunoglobulin deficienc$ or hypogammaglobulin$)).ti,ab,kf.
15	acquired hypogammaglobulin$.ti,ab,kf.
16	cryoglobulin?em$.ti,ab,kf.
17	((autoimmune or failure$) adj3 (polyglandular$ or polyendocrin$)).ti,ab,kf.
18	(progeria or hutchinson-gilford$).ti,ab,kf.
19	tyrosin?em$.ti,ab,kf.
20	(maple syrup urine or msud).ti,ab,kf.
21	branched chain.ti,ab,kf.
22	(bckd adj5 (deficienc$ or ketoacid$ or keto-acid$)).ti,ab,kf.
23	hyperleucine-isoleucin$.ti,ab,kf.
24	(methylmalonic acid?emi$ or methylmalonic aciduri$ or methyl malonic acid?emi$ or methyl malonic aciduri$).ti,ab,kf.
25	(propionic acid?em$ or propionic acidur$ or propionyl-CoA carboxylase deficienc$ or ketotic glycin?em$).ti,ab,kf.
26	(adrenoleukodystroph$ or x-ald or schilder-addison$ or addison-schilder$ or adrenomyeloneuropath$).ti,ab,kf.
27	((carnitine palmityltransferase or carnitine palmitoyltransferase or carnitine o-palmityltransferase or carnitine o-palmitoyltransferase) adj3 deficienc$).ti,ab,kf.

28	(fanconi$ adj (syndrome$ or disease$ or disorder$)).ti,ab,kf.
29	(ocular adj3 (renal or kidney)).ti,ab,kf.
30	(cystinos$ or cystine storage or cystine diathes$ or cystine disease$).ti,ab,kf.
31	((lowe or lowes or oculocerebrorenal or cerebrooculorenal or cerebro-oculo-renal) adj3 (syndrome$ or disease$ or disorder$)).ti,ab,kf.
32	(molybdenum cofactor deficien$ or molybdenum co-factor deficien$).ti,ab,kf.
33	((sulphite$ or sulfite$) adj3 oxidase deficien$).ti,ab,kf.
34	(argininosuccinic acidur$ or argininosuccinic acid?emi$).ti,ab,kf.
35	(citrullin?emi$ or citrullinuri$).ti,ab,kf.
36	(glutaric acid?emi$ or glutaric aciduri$).ti,ab,kf.
37	(glycine encephalopath$ or non-ketotic hyperglycin?emi$ or nonketotic hyperglycin?emi$).ti,ab,kf.
38	(arginin?emi$ or arginase deficien$ or hyperarginin?emi$).ti,ab,kf.
39	(aminoaciduri$ or aminoacid?emi$).ti,ab,kf.
40	(glycogen storage adj (disease$ or syndrome$ or disorder$)).ti,ab,kf.
41	(pompe$ adj (disease$ or syndrome$ or disorder$)).ti,ab,kf.
42	galactos?emi$.ti,ab,kf.
43	(pyruvate dehydrogenase adj3 deficien$).ti,ab,kf.
44	(oxalosis and (renal or kidney$)).ti,ab,kf.
45	gangliosidos$.ti,ab,kf.
46	(sandhoff$ adj (disease$ or syndrome$ or disorder$)).ti,ab,kf.
47	tay sach$.ti,ab,kf.
48	mucolipidos$.ti,ab,kf.
49	(canavan$ leucodystroph$ or aspartoacylase deficien$ or aminoacylase 2 deficien$).ti,ab,kf.
50	((canavan$ or canavan-van bogaert-bertrand$) adj (disease$ or syndrome$ or disorder$)).ti,ab,kf.
51	(gaucher$ adj (disease$ or syndrome$ or disorder$)).ti,ab,kf.
52	(glucocerebrosidase deficien$ or glucosylceramidase deficien$).ti,ab,kf.
53	(metachromatic leukodystroph$ or arylsulfatase A deficien$ or metachromic leukodystroph$).ti,ab,kf.
54	(niemann-pick$ or sphingomyelinase deficien$).ti,ab,kf.
55	sphingolipidos$.ti,ab,kf.
56	(fabry$ adj (disease$ or syndrome$ or disorder$)).ti,ab,kf.
57	(angiokeratoma corporis diffusum or alpha-galactosidase A deficien$).ti,ab,kf.
58	(krabbe$ adj (disease$ or syndrome$ or disorder$)).ti,ab,kf.
59	(globoid cell leukodystroph$ or galactosylceramide lipidos$ or galactosylcerebrosidase deficien$ or galactosylceramidase deficien$).ti,ab,kf.
60	(farber$ adj (disease$ or syndrome$ or disorder$)).ti,ab,kf.
61	(farber$ lipogranulomatos$ or ceramidase deficien$ or fibrocytic dysmucopolysaccharidos$).ti,ab,kf.
62	pelizaeus-merzbacher$.ti,ab,kf.
63	(sulfatase deficien$ or sulphatase deficien$ or mucosulfatidos$).ti,ab,kf.
64	(austin$ adj (disease$ or syndrome$ or disorder$)).ti,ab,kf.
65	sulfatidos$.ti,ab,kf.
66	sea-blue histiocyt$.ti,ab,kf.

67	(batten$ adj (disease$ or syndrome$ or disorder$)).ti,ab,kf.
68	(neuronal ceroid lipofuscinos$ or santavuori-haltia$ or jansky-bielschowsky$ or bielschowsky-jansky$).ti,ab,kf.
69	(kuf$ adj (disease$ or syndrome$ or disorder$)).ti,ab,kf.
70	spielmeyer vogt$.ti,ab,kf.
71	((cerebrotendineous or cerebrotendinous or cerebrotendious or cerebral) adj3 (xanthomatos$ or cholesteros$)).ti,ab,kf.
72	bogaert-scherer-epstein$.ti,ab,kf.
73	(wolman$ adj (disease$ or syndrome$ or disorder$)).ti,ab,kf.
74	lysosomal acid lipase deficien$.ti,ab,kf.
75	mucopolysaccharidos$.ti,ab,kf.
76	(hurler$ adj2 (syndrome$ or disease$ or disorder$)).ti,ab,kf.
77	(hunter$ adj2 (syndrome$ or disease$ or disorder$)).ti,ab,kf.
78	(MPS1 or MPS2 or MPS3 or MPS4 or MPS5 or MPS6 or MPS7 or MPS-1 or MPS-2 or MPS-3 or MPS-4 or MPS-5 or MPS-6 or MPS-7 or MPSI or MPSII or MPSIII or MPSIV or MPSV or MPSVI or MPSVII or MPS-I or MPS-II or MPS-III or MPS-IV or MPS-V or MPS-VI or MPS-VII).ti,ab,kf.
79	(beta glucuronidase deficien$ or sly syndrome$ or sly disorder$ or sly disease$).ti,ab,kf.
80	(maroteaux-lamy$ or marotaeux-lamy$ or polydystrophic dwarfism).ti,ab,kf.
81	(morquio$ or moriquio$ or beta galactosidase deficien$).ti,ab,kf.
82	(sanfilippo$ or sanfillipo$).ti,ab,kf.
83	(mucolipidos$ or pseudo-hurler$ or pseudohurler$).ti,ab,kf.
84	((inclusion-cell or i-cell) adj (disease$ or syndrome$ or disorder$)).ti,ab,kf.
85	(fucosidos$ or fucidos$).ti,ab,kf.
86	((cdg or ctg) adj (disease$ or disorder$ or syndrome$)).ti,ab,kf.
87	(carbohydrate-deficient glycoprotein adj (disease$ or disorder$ or syndrome$)).ti,ab,kf.
88	(congenital disorder$ adj3 glycosylation).ti,ab,kf.
89	juvenile gout.ti,ab,kf.
90	menkes$.ti,ab,kf.
91	((copper transport or steely hair or kinky hair) adj (disease$ or syndrome$ or disorder$)).ti,ab,kf.
92	(antitrypsin deficien$ or A1AD).ti,ab,kf.
93	(AAT deficien$ or alpha-1 protease deficien$).ti,ab,kf.
94	bisalbumin?emi$.ti,ab,kf.
95	(congenital generali?ed lipodystroph$ or berardinelli$ or bernardnelli$).ti,ab,kf.
96	(landau-kleffner$ or infantile acquired aphasia$ or acquired epileptic aphasia$).ti,ab,kf.
97	(aphasia$ adj5 convulsive).ti,ab,kf.
98	Rett Syndrome/
99	(rett$ adj (syndrome$ or disease$ or disorder$)).ti,ab,kf.
100	cerebroatrophic hyperammon?emi$.ti,ab,kf.
101	Huntingtons Disease/
102	huntington$.ti,ab,kf.
103	((nyhan$ or kelley-seegmiller$) adj (syndrome$ or disorder$ or disease$)).ti,ab,kf.

104	(spinocerebellar ataxia$ or ataxia$ telangiectasia$ or louis-bar$ syndrome$ or louis-bar$ disease$ or louis-bar$ disorder$ or machado-joseph$ or joseph$ disease$ or joseph$ disorder$ or joseph$ syndrome$).ti,ab,kf.
105	((friedreich$ or friedrich$) adj3 ataxia$).ti,ab,kf.
106	spinocerebellar degenerat$.ti,ab,kf.
107	(spinal muscular atroph$ or werdnig hoffman$).ti,ab,kf.
108	(dubowitz$ or kugelberg-welander$).ti,ab,kf.
109	(fazio-londe$ or faziolonde$ or progressive bulbar pals$).ti,ab,kf.
110	parkinsons disease/
111	(parkinson$ or hypokinetic rigid syndrome$ or hypokinetic rigid disease$ or hypokinetic rigid disorder$ or paralysis agitan$ or shaking pals$).ti,ab,kf.
112	(pantothenate kinase-associated neurodegenerat$ or PKAN or hallervorden-spatz$).ti,ab,kf.
113	((neurodegeneration adj3 brain iron accumulation) or NBIA$1).ti,ab,kf.
114	(olivopontocerebellar atroph$ or OPCA or olivopontocerebellar degenerat$).ti,ab,kf.
115	(multiple system atrophy adj5 cerebellar).ti,ab,kf.
116	(alper$ adj (disease$ or syndrome$ or disorder$)).ti,ab,kf.
117	(progressive sclerosing poliodystroph$ or progressive infantile poliodystroph$).ti,ab,kf.
118	(diffuse cerebral sclerosis adj5 schilder$).ti,ab,kf.
119	(leigh$ adj (syndrome$ or disease$ or disorder$)).ti,ab,kf.
120	(subacute necrotizing encephalomyelopath$ or subacute necrotising encephalomyelopath$ or sub-acute necrotizing encephalomyelopath$ or sub-acute necrotising encephalomyelopath$ or SNEM).ti,ab,kf.
121	(aicardi-gouti?res or aicardia-gouti?res).ti,ab,kf.
122	(worster-drought$ or congenital suprabulbar pares$).ti,ab,kf.
123	multiple sclerosis/
124	(multiple sclerosis or disseminated sclerosis or encephalomyelitis disseminata$).ti,ab,kf.
125	(demyelinating adj (disease$ or syndrome$ or disorder$)).ti,ab,kf.
126	myoclonic epileps$.ti,ab,kf.
127	((lafora$ or merrf$ or unverricht-lundborg$ or janz$) adj (disease$ or syndrome$ or disorder$)).ti,ab,kf.
128	lennox-gastaut$.ti,ab,kf.
129	(lennox$ adj (syndrome$ or disease$ or disorder$)).ti,ab,kf.
130	(west$ adj (syndrome$ or disease$ or disorder$)).ti,ab,kf.
131	(epilepsia partialis continua or kojevnikov$ or epilepsia partialis continuoa or kozhevnikof$).ti,ab,kf.
132	Charcot-Marie-Tooth Disease/
133	(charcot-marie-tooth$ or peroneal muscular atroph$).ti,ab,kf.
134	(progressive neuropathic muscular atroph$ or hereditary peroneal nerve dysfunction$ or peroneal neuropath$).ti,ab,kf.
135	(hereditary sensory adj3 motor neuropath$).ti,ab,kf.
136	(hereditary motor adj3 sensory neuropath$).ti,ab,kf.
137	(infantile refsum or infantile phytanic acid storage).ti,ab,kf.
138	congenital myasth?eni$.ti,ab,kf.
139	(duchenne muscular dystroph$ or dmd).ti,ab,kf.

140	(limb-girdle or erb$ muscular dystroph$).ti,ab,kf.
141	(sarcoglycanopath$ or sarcoglycaopath$).ti,ab,kf.
142	(osteochondrodysplas$ or schwartz-jampel or chondrodystrophi$ myotoni$ or myotoni$ chondrodystrophi$).ti,ab,kf.
143	(congenita$ myotoni$ or myotoni$ congenita$).ti,ab,kf.
144	(thomsen$ adj (disease$ or disorder$ or syndrome$)).ti,ab,kf.
145	((recessive adj3 myotoni$) or becker$ myotoni$).ti,ab,kf.
146	(isaac$ adj (syndrome$ or disease$ or disorder$)).ti,ab,kf.
147	neuromyotoni$.ti,ab,kf.
148	(paramyotoni$ congenita$ or congenita$ paramyotoni$).ti,ab,kf.
149	(eulenburg$ adj (disease$ or syndrome$ or disorder$)).ti,ab,kf.
150	(myotoni$ adj (disease$ or disorder$ or syndrome$)).ti,ab,kf.
151	pseudomyotoni$.ti,ab,kf.
152	(congenital adj3 myopath$).ti,ab,kf.
153	myopathycongenital.ti,ab,kf.
154	((nemaline or rod) adj3 myopath$).ti,ab,kf.
155	((central core or mini-core or minicore or multicore or multi-core) adj (disease$ or disorder$ or syndrome$ or myopath$)).ti,ab,kf.
156	fiber type disproportion.ti,ab,kf.
157	fibre type disproportion.ti,ab,kf.
158	(congenital$ adj5 muscular dystroph$).ti,ab,kf.
159	((centronuclear or myotubular) adj myopath$).ti,ab,kf.
160	(mitochondrial myopath$ or mitochondrial encephalomyopath$ or chronic progressive external ophthalmopleg$).ti,ab,kf.
161	((melas or kearns-sayre$) adj (syndrome$ or disease$ or disorder$)).ti,ab,kf.
162	Quadriplegia/ and spastic$.ti,ab,kf.
163	(spastic quadriplegi$ or spastic tetraplegi$).ti,ab,kf.
164	(reye$ adj (syndrome$ or disease$ or disorder$)).ti,ab,kf.
165	multiple pterygium.ti,ab,kf.
166	((primary pulmonary or precapillary pulmonary or idiopathic pulmonary) adj (hypertension or ht or arterial hypertension)).ti,ab,kf.
167	((primary bronchopulmonary or precapillary bronchopulmonary or idiopathic bronchopulmonary) adj (hypertension or ht or arterial hypertension)).ti,ab,kf.
168	((primary lung or precapillary lung or idiopathic lung) adj (hypertension or ht or arterial hypertension)).ti,ab,kf.
169	ipah.ti,ab,kf.
170	((congestive or dilated) adj cardiomyopath$).ti,ab,kf.
171	(hypertrophic adj cardiomyopath$).ti,ab,kf.
172	(congenital adj3 cardiomyopath$).ti,ab,kf.
173	(restrictive cardiomyopath$ or obliterative cardiomyopath$ or constrictive cardiomyopath$).ti,ab,kf.
174	(pulmonary fibros$ or lung fibros$ or bronchopulmonary fibros$ or fibrosing alveolit$ or interstitial pneumonit$).ti,ab,kf.
175	(respiratory adj (failure$ or insufficienc$)).ti,ab,kf.
176	((cystic lung or cystic pulmonary or cystic bronchopulmonary) adj (disease$ or disorder or syndrome$)).ti,ab,kf.
177	(bronchogenic cyst$ or bronchopulmonary foregut malformation$).ti,ab,kf.

178	cystic adenomatoid malformation$.ti,ab,kf.
179	lobar emphysem$.ti,ab,kf.
180	(pulmonary sequestration$ or bronchopulmonary sequestration$ or lung sequestration$ or extralobar sequestration$ or extra-lobar sequestration$ or intralobar sequestration$ or intra-lobar sequestration$).ti,ab,kf.
181	pulmolithias$.ti,ab,kf.
182	((liver$1 or hepatic) adj3 fail$).ti,ab,kf.
183	exp "Cirrhosis (Liver)"/
184	(cirrhosis adj3 liver$1).ti,ab,kf.
185	((veno-occlusive or venous occlusive) adj (disease$ or syndrome$ or disorder$)).ti,ab,kf.
186	(swachman-diamond or shwachman-bodian or schwachmann-diamond or shwachmann-bodian).ti,ab,kf.
187	wegener$ granulomatos$.ti,ab,kf.
188	(granulomatos$ adj3 polyangiit$).ti,ab,kf.
189	essential osteolys$.ti,ab,kf.
190	((gorham$ or gorham-stout$ or vanishing bone or phantom bone) adj (disease$ or syndrome$ or disorder)).ti,ab,kf.
191	((arc or arthrogryposis renal dysfunction cholestasis) adj (disease$ or syndrome$ or disorder)).ti,ab,kf.
192	Cerebral Hemorrhage/ and congen$.mp.
193	Cerebral Hemorrhage/ and Birth Injuries/
194	(cerebral h?emorrhage$ and (birth$ adj3 injur$)).ti,ab,kf.
195	asphyxia neonatorum.ti,ab,kf.
196	((perinatal$ or neonatal$ or birth$) adj3 asphyxia$).ti,ab,kf.
197	congenital rubella.ti,ab,kf.
198	(congenital adj (cytomegalovirus$ or cmv)).ti,ab,kf.
199	Herpesvirus 3, Human/ and congenital$.ti,ab,kf.
200	((congenital or fetal or foetal) adj3 (varicella$ or chicken pox$ or VZV)).ti,ab,kf.
201	congenital toxoplasmos$.ti,ab,kf.
202	((brain$ or cerebral) adj3 hypoxi$).ti,ab,kf.
203	(congenital$ adj3 (kidney failure$ or renal failure$ or kidney insufficienc$ or renal insufficienc$)).ti,ab,kf.
204	(congenital$ adj3 (kidney disease$ or renal disease$)).ti,ab,kf.
205	Anencephaly/
206	(anencephal$ or meroanencephal$ or craniorachischis$).ti,ab,kf.
207	(aprosencephal$ adj3 open cranium).ti,ab,kf.
208	(encephalocele$ or cranium bifidum).ti,ab,kf.
209	dandy-walker$.ti,ab,kf.
210	(acrocallosal or acro-callosal or acrocolossal or acro colossal).ti,ab,kf.
211	(aicardi$ adj (syndrome$ or disease$ or disorder$)).ti,ab,kf.
212	(holoprosencephal$ or arhinencephal$ or holosprosencephal$).ti,ab,kf.
213	(hydranencephal$ or hydrancephal$ or hydroanencephal$).ti,ab,kf.
214	Microcephaly/
215	(lissencephal$ or walker-warburg$ or miller-dieker$ or norman-robert$ or microlissencephal$).ti,ab,kf.

216	((fukuyama$ or muscle-eye-brain) adj (syndrome$ or disease$ or disorder$)).ti,ab,kf.
217	(microgyria$ or microgyrus or micro-gyria$ or micro-gyrus).ti,ab,kf.
218	(pachygyria$ or pachgyria$).ti,ab,kf.
219	agyria$.ti,ab,kf.
220	((septo-optic or septooptic) adj dysplas$).ti,ab,kf.
221	de morsier$.ti,ab,kf.
222	(schizencephal$ or schizzencephal$).ti,ab,kf.
223	chiari$ malformation$.ti,ab,kf.
224	(truncus or common arterial trunk$).ti,ab,kf.
225	((transposition$ or dextrotransposition$ or dtransposition$ or levotransposition$ or ltransposition$) adj3 (great arter$ or main arter$ or aorta$ or pulmonary arter$ or great vessel$ or main vessel$)).ti,ab,kf.
226	(dextro-tga or d-tga or levo-tga or l-tga).ti,ab,kf.
227	(double inlet adj3 ventricle$).ti,ab,kf.
228	DILV.ti,ab,kf.
229	single ventricle$.ti,ab,kf.
230	(isomerism adj3 atrial appendage$).ti,ab,kf.
231	(aspleni$ or polyspleni$ or poly-spleni$).ti,ab,kf.
232	(tetralogy adj3 fallot$).ti,ab,kf.
233	(eisenmenger$ or tardive cyanos$ or eisenmeyer$).ti,ab,kf.
234	(pentalogy adj3 fallot$).ti,ab,kf.
235	((pulmonary or bronchopulmonary or lung$) adj3 atresia$).ti,ab,kf.
236	((tricuspid or tri) adj3 atresia$).ti,ab,kf.
237	(ebstein$ adj (anomal$ or malformation$)).ti,ab,kf.
238	(hypoplastic left heart adj (syndrome$ or disease$ or disorder$)).ti,ab,kf.
239	((aortic or aorta$) adj3 atresia$).ti,ab,kf.
240	(mitral adj3 atresia$).ti,ab,kf.
241	((absence$ or absent$) adj3 (aorta$ or aortic)).ti,ab,kf.
242	(aplas$ adj3 (aorta$ or aortic)).ti,ab,kf.
243	(((aorta$ or aortic) adj3 aneurys$) and congenital$).ti,ab,kf.
244	(hypoplas$ adj3 (aorta$ or aortic)).ti,ab,kf.
245	(convulsion$ adj3 (aorta$ or aortic)).ti,ab,kf.
246	(persistent right adj3 (aorta$ or aortic)).ti,ab,kf.
247	((anomalous pulmonary venous or anamolous pulmonary venous) adj (connection or drainage or return)).ti,ab,kf.
248	((absence$ or absent$) adj3 vena$ cava$).ti,ab,kf.
249	(persistent left adj3 cardinal vein$).ti,ab,kf.
250	((scimitar$ or pulmonary venolobar) adj (syndrome$ or disease$ or disorder$)).ti,ab,kf.
251	(arteriovenous malformations/ or intracranial arteriovenous malformations/) and bilateral.ti,ab,kf.
252	((bilateral AV or bilateral arteriovenous or bilateral arterio-venous) adj3 malform$).ti,ab,kf.
253	((trachea$ or windpipe$ or wind-pipe$) adj3 atresia$).ti,ab,kf.
254	((trachea$ or laryngotrachea$ or glottic or subglottic or sub-glottic) adj3 stenosis).ti,ab,kf.

255	((lung$ or pulmonary or bronchopulmonary) adj3 (hypoplas$ or dysplas$)).ti,ab,kf.
256	((absence$ or absent$) adj3 (esophag$ or oesophag$ or foodpipe or food-pipe$ or gullet$)).ti,ab,kf.
257	(duoden$ adj3 atresia$).ti,ab,kf.
258	((absence$ or absent$) adj3 (intestin$ or gastrointestin$)).ti,ab,kf.
259	((intestin$ or gastrointestin$) adj3 atresia$).ti,ab,kf.
260	((intestin$ or gastrointestin$) adj3 stenos$).ti,ab,kf.
261	(cloaca$ adj3 (abnor$ or malform$ or anomal$)).ti,ab,kf.
262	(cloaca$ adj3 exopthalmo$).ti,ab,kf.
263	(biliary adj3 atresia$).ti,ab,kf.
264	(extrahepatic ductopen$ or extra-hepatic ductopen$ or progressive obliterative cholangiopath$).ti,ab,kf.
265	(biliary adj3 hypoplas$).ti,ab,kf.
266	(alagille$ adj3 atresia$).ti,ab,kf.
267	((absence$ or absent$) adj3 kidney$).ti,ab,kf.
268	(potter$ adj (sequence$ or syndrome$ or disease$ or disorder$)).ti,ab,kf.
269	oligohydramn$.ti,ab,kf.
270	((kidney$ or renal) adj3 dysplas$).ti,ab,kf.
271	((meckel$ or meckelgruber$ or gruber$) adj (syndrome$ or disease$ or disorder$)).ti,ab,kf.
272	dysencephalia splanchnocystica$.ti,ab,kf.
273	(pena-shokeir$ or penn-shokeir$).ti,ab,kf.
274	(larsen$ adj (syndrome$ or disease$ or disorder$)).ti,ab,kf.
275	acrocephalosyndactyl$.ti,ab,kf.
276	(pfeiffer$ adj (syndrome$ or disease$ or syndrome$)).ti,ab,kf.
277	short rib$1.ti,ab,kf.
278	(saldino-noonan$ or majewski$ or verma-naumoff$ or beemer-langer$).ti,ab,kf.
279	(jeune$ adj (syndrome$ or disease$ or disorder$)).ti,ab,kf.
280	asphyxiating thoracic dysplas$.ti,ab,kf.
281	chondrodysplasia punctata$.ti,ab,kf.
282	((conradi$ or h?nermann$ or happle$) adj3 (syndrome$ or disease$ or disorder$)).ti,ab,kf.
283	osteogenesis imperfecta.ti,ab,kf.
284	((brittle bone or lobstein$) adj (disease$ or disorder$ or syndrome$)).ti,ab,kf.
285	(spondyloepimetaphyseal or spondyloepiphyseal or spendylo metaphyseal).ti,ab,kf.
286	(omphalocele$ or omphalocoele$ or exomphalos).ti,ab,kf.
287	(hernia$ adj3 umbilic$).ti,ab,kf.
288	gastroschis$.ti,ab,kf.
289	(lamellar$ adj3 ichthyos$).ti,ab,kf.
290	((harlequin$ or harloquin$) adj3 (ichthyos$ or baby or babies or f?etus$)).ti,ab,kf.
291	(ichthyosis congenita$ or ichthyosis fetalis or keratosis diffusa fetalis).ti,ab,kf.
292	epidermolysis bullosa$.ti,ab,kf.
293	(johanson-blizzard$ or johanna-blizzard$).ti,ab,kf.
294	xeroderma pigmentosum.ti,ab,kf.
295	lacrimo-auriculo-dento-digital.ti,ab,kf.

296	ectodermal dysplas$.ti,ab,kf.
297	((ladd or eec) adj (syndrome$ or disease$ or disorder$)).ti,ab,kf.
298	(sturge-weber or encephalotrigeminal angiomatos$).ti,ab,kf.
299	Fetal Alcohol Syndrome/
300	f?etal alcohol.ti,ab,kf.
301	pierre robin$.ti,ab,kf.
302	(acrocephalosyndact$ or acrocephalopolysyndact$).ti,ab,kf.
303	((apert$ or crouzon$ or saethre-chotzen$ or noack$ or carpenter$ or sakati-nyhan-tisdale$ or goodman$) adj (syndrome$ or disorder$ or disease$)).ti,ab,kf.
304	(fraser$ adj (syndrome$ or disease$ or disorder$)).ti,ab,kf.
305	cryptophthalmos.ti,ab,kf.
306	(cyclopia$1 or cyclocephal$ or synophthalmi$).ti,ab,kf.
307	(goldenhar$ or oculo-auriculo-vertebral).ti,ab,kf.
308	((m?bius$ or moebius$) adj (syndrome$ or disease$ or disorder$)).ti,ab,kf.
309	(orofaciodigital or oro-facial-digital or oral-facial-digital or papillon-league$ or psaume$).ti,ab,kf.
310	(robin$ adj (syndrome$ or disorder$ or disease$)).ti,ab,kf.
311	(freeman-sheldon$ or distal arthrogrypos$ or craniocarpotarsal dysplas$ or craniocarpotarsal dystroph$ or canio-carpo-tarsal or windmill-vane-hand$ or whistling-face).ti,ab,kf.
312	Cornelia De Lange Syndrome/
313	((de lange$ or bushy$) adj (syndrome$ or disorder$ or disease$)).ti,ab,kf.
314	amsterdam dwarfism.ti,ab,kf.
315	(aarskog or faciodigitogenital or facio-digito-genital or facial digital genital or shawl scrotum or faciogenital or facio-genital).ti,ab,kf.
316	(cockayne$ or neill-dingwall$).ti,ab,kf.
317	(cerebro-oculo-facio-skeletal or cerebro-oculo-facial-skeletal).ti,ab,kf.
318	(dubowitz$ adj (syndrome$ or disease$ or disorder$)).ti,ab,kf.
319	(robinow$ or robinhow$).ti,ab,kf.
320	(f?etal face or f?etal facies or f?etal faces or acral dysostos$ or mesomelic dwarfism or covesdem$).ti,ab,kf.
321	(silver-russell$ or russell-silver$).ti,ab,kf.
322	(silver$ adj (syndrome$ or disease$ or disorder$)).ti,ab,kf.
323	((seckel$ or harper$) adj (syndrome$ or disease$ or disorder$)).ti,ab,kf.
324	(microcephalic primordial dwarfism or bird-headed dwarf$ or virchow-seckel dwarfism).ti,ab,kf.
325	(smith-lemli-opitz$ or dehydrocholesterol reductase deficien$).ti,ab,kf.
326	Prader Willi Syndrome/
327	(prader-willi$ or pradar-willi$).ti,ab,kf.
328	(rubinstein-taybi$ or rubenstein-tabyii$ or broad thumb-hallux).ti,ab,kf.
329	((rubinstein$ or rubenstein$) adj2 (syndrome$ or disease$ or disorder$)).ti,ab,kf.
330	(alport$ adj (syndrome$ or disease$ or disorder$)).ti,ab,kf.
331	(hereditary nephritis or h?emorrhagic familial nephritis).ti,ab,kf.
332	(hereditary deafness adj3 nephropath$).ti,ab,kf.
333	(h?ematuria adj3 nephropath$ adj3 deafness).ti,ab,kf.
334	laurence-moon$.ti,ab,kf.

335	(bardet-biedl$ or biedl-bardet$).ti,ab,kf.
336	zellweger$.ti,ab,kf.
337	((cerebrohepatorenal or cerebro-hepato-renal) adj (syndrome$ or disease$ or disorder$)).ti,ab,kf.
338	(edward$ adj (syndrome$ or disease$ or disorder$)).ti,ab,kf.
339	"trisomy 18".ti,ab,kf.
340	(patau$ adj (syndrome$ or disease$ or disorder$)).ti,ab,kf.
341	("trisomy 13" or "trisomy D").ti,ab,kf.
342	"trisomy 22".ti,ab,kf.
343	"trisomy 9".ti,ab,kf.
344	"trisomy 10".ti,ab,kf.
345	duplication syndrome$.ti,ab,kf.
346	(("chromosome 8" or "chr 8") adj5 duplicat$).ti,ab,kf.
347	(("chromosome x" or "chr x") and duplicat$).ti,ab,kf.
348	(chromosom$ abnormality adj5 duplicat$).ti,ab,kf.
349	"tetrasomy 5p".ti,ab,kf.
350	(tetrasomy adj3 mosaic$).ti,ab,kf.
351	(delet$ adj5 short arm adj5 "chrom$ 4").ti,ab,kf.
352	((wolf-hirschhorn$ or wolff hirschorn$ or chromosome deletion dillan$ or pitt-rogers-dank$ or pitt$) adj3 (syndrome$ or disease$ or disorder$)).ti,ab,kf.
353	Crying Cat Syndrome/
354	((cri du chat$ or crying cat$ or 5p or lejeune$) adj3 (syndrome$ or disease$ or disorder$)).ti,ab,kf.
355	((jacobsen$ or 11q deletion) adj5 (syndrome$ or disease$ or disorder$)).ti,ab,kf.
356	(9p minus or 9p deletion).ti,ab,kf.
357	(alfi$ adj (syndrome$ or disease$ or disorder$)).ti,ab,kf.
358	(degouchy$ or de gouchy$ or degrouchy$ or de grouchy$).ti,ab,kf.
359	distal 18q.ti,ab,kf.
360	(ondine$ curse or congenital central hypoventilation or primary alveolar hypoventilation).ti,ab,kf.
361	(((graft vs host or graft versus host) adj (disease$ or syndrome$ or disorder)) and chronic$).ti,ab,kf.
362	Terminally Ill Patients/
363	Palliative Care/
364	Hospice/
365	(life adj2 limit$).ti,ab,kf.
366	(life adj2 threaten$).ti,ab,kf.
367	end of life.ti,ab,kf.
368	eol.ti,ab,kf.
369	(terminal$ adj2 (ill or illness$ or condition$1 or disease$1 or syndrome$ or disorder$)).ti,ab,kf.
370	(terminal adj2 (care$ or caring)).ti,ab,kf.
371	palliat$.ti,ab,kf.
372	(care adj2 dying).ti,ab,kf.
373	(technology adj2 dependent).ti,ab,kf.
374	hospice$.ti,ab,kf.

375	(severe adj2 (need or needs or illness$ or disease$1 or disabilit$ or impairment$1 or impediment$1 or condition$1 or disadvant$ or problem$1 or syndrome$1 or disorder$1)).ti,ab,kf.
376	(complex adj2 (need or needs or illness$ or disease$1 or disabilit$ or impairment$1 or impediment$1 or condition$1 or disadvant$ or problem$1 or syndrome$1 or disorder$1)).ti,ab,kf.
377	(rare adj2 (illness$ or disease$ or disabilit$ or impairment$ or impediment$ or condition$1 or syndrome$1 or disorder$1)).ti,ab,kf.
378	(multiple adj2 (need or needs or illness$ or disease$1 or disabilit$ or impairment$1 or impediment$ or condition$1 or disadvant$ or health or syndrome$1 or disorder$1)).ti,ab,kf.
379	(profound adj2 (need or needs or illness$ or disease$ or disabilit$ or impairment$ or impediment$ or condition$1 or syndrome$1 or disorder$1)).ti,ab,kf.
380	(intense adj2 (need or needs or illness$ or disease$ or disabilit$ or impairment$ or impediment$ or condition$1 or syndrome$1 or disorder$1)).ti,ab,kf.
381	(serious adj2 (disabilit$ or impairment$ or impediment$ or condition$1 or disadvant$)).ti,ab,kf.
382	exp HIV/
383	(HIV or human immunodeficiency virus$).ti,ab,kf.
384	(htlv or human t-lymphotropic virus$ or human t cell lymphotropic virus$).ti,ab,kf.
385	(acquired immune deficiency syndrome$ or acquired immunodeficiency syndrome$).ti,ab,kf.
386	(AIDS adj3 (virus$ or infection$)).ti,ab,kf.
387	(AIDS adj (related or associated)).ti,ab,kf.
388	exp Neoplasms/
389	(cancer$ or carcin$ or tumor$ or tumour$ or neoplas$ or adenocarcin$ or oncol$ or malignan$).ti,ab,kf.
390	Cystic Fibrosis/
391	(cystic fibrosis or fibrocystic or fibro-cystic or mucoviscidosis or cf).ti,ab,kf.
392	Cerebral Palsy/
393	(cerebr$ adj3 pals$).ti,ab,kf.
394	spasticit$.ti,ab,kf.
395	Quadriplegia/
396	(spastic$ and (quadripleg$ or tetrapleg$)).ti,ab,kf.
397	((kidney$ or renal) adj3 (failure$ or insufficienc$)).ti,ab,kf.
398	(end stage adj3 (kidney or renal)).ti,ab,kf.
399	(("stage 5" or "stage V") adj3 (kidney or renal)).ti,ab,kf.
400	(ESRD or ESKD or ESRF or ESKF or CRF or CKF).ti,ab,kf.
401	or/1-400
402	((Young adj1 people$) or Youth$ or Care leaver$ or residential child$ or Adolescen$ or Young adult$ or Young person$ or Young men$ or Young women$ or Teen$ or juvenile$ or Younger people or Youngster$ or Looked after or Child welfare or paediatric$ or pediatric$ or peadiatric$ or Young male$ or Young female$ or juvenile or children$ or child or childhood or (young adj1 patient$) or young carer$ or minors or puber$ or pubescen$ or ((secondary or high*) adj2 (school* or education))).ti,ab.
403	pediatrics/
404	402 or 403

405	((transition$ or transfer$ or handoff or handover or hand over) and (Service$ or care or clinic$ or healthcare or hospital$ or center$ or centre$ or facility or facilities or unit$ or department$ or institution$ or agency or agencies or hospice$ or provider$ or program$ or Coordinat$ or Framework$ or Managing or Managed or preparedness or Planning or Preparing or Preparation$ or Plan$ or Protocol$ or planned or Support or Supporting or Trajectory or Trajectories or Pathway$ or Process or Processes or Readiness or Partnership$ or programme$ or program$ or training or strateg$ or Failure$ or Barrier$ or system?)).ti.
406	((transition$ or transfer$ or handoff or handover or hand over) adj3 (Service$ or care or clinic$ or healthcare or hospital$ or center$ or centre$ or facility or facilities or unit$ or department$ or institution$ or agency or agencies or hospice$ or provider$ or program$ or Coordinat$ or Framework$ or Managing or Managed or preparedness or Planning or Preparing or Preparation$ or Plan$ or Protocol$ or planned or Support or Supporting or Trajectory or Trajectories or Pathway$ or Process or Processes or Readiness or Partnership$ or programme$ or program$ or training or strateg$ or Failure$ or Barrier$ or system?)).ab.
407	(continu$ and (care or healthcare or Support or Supporting or Failure$ or Barrier$)).ti.
408	(continu$ adj3 (care or healthcare or Support or Supporting or Failure$ or Barrier$)).ab.
409	Continuum of Care/
410	patient handoff/
411	Treatment Planning/
412	Patient transfer/
413	(transition$ or transfer$ or handoff or handover or hand$ over).ti,ab.
414	(409 or 411) and 413
415	or/405-408,410,412,414
416	401 and 404 and 415
417	limit 416 to (english language and yr="1990 -Current")

CINAHL (EBSCOHost)

Concepts:

1. LLC: lines 1-525
2. Child/young adult: lines 526-536
3. Transition: lines 537-547

1	MH "Creutzfeldt-Jakob Syndrome"
2	TI (creutzfeldt-jakob* or jakob-creutzfeldt* or cjd or spongiform encephalopath*) OR AB ((creutzfeldt-jakob* or jakob-creutzfeldt* or cjd or spongiform encephalopath*)
3	MH “Subacute Sclerosing Panencephalitis”
4	TI (subacute sclerosing panencephalit* or sub-acute sclerosing panencephalit* or sspe or subacute sclerosing leukoencephalit* or sub-acute sclerosing leukoencephalit* or van bogaert* leukoencephalit* or measles inclusion body encephalit* or mibe) OR AB (subacute sclerosing panencephalit* or sub-acute sclerosing panencephalit* or sspe or subacute sclerosing leukoencephalit* or sub-acute sclerosing leukoencephalit* or van bogaert* leukoencephalit* or measles inclusion body encephalit* or mibe)
5	MH "beta-Thalassemia"
6	TI (beta N (thalass#emi* or thalas#emi*)) OR AB (beta N (thalass#emi* or thalas#emi*))
7	TI ((thalass#emi* or thalas#emi*) N1 major) OR AB ((thalass#emi* or thalas#emi*) N1 major)
8	MH “Anemia, Aplastic”
9	TI ((hypoplastic or aplastic) N1 an#emi*) OR AB ((hypoplastic or aplastic) N1 an#emi*)
10	TI (medullary N3 hypoplas*) OR AB (medullary N3 hypoplas*)
11	MH "Neutropenia+"
12	TI ((severe or chronic*) N3 neutropeni*) OR AB ((severe or chronic*) N3 neutropeni*)
13	MH "immunologic deficiency syndromes" OR MH "acquired immunodeficiency syndrome"
14	TI (immun* deficiency N1 (syndrome* or disease* or disorder*)) OR AB (immun* deficiency N1 (syndrome* or disease* or disorder*))
15	TI (immunodeficiency N1 (syndrome* or disease* or disorder*)) OR AB (immunodeficiency N1 (syndrome* or disease* or disorder*))
16	MH "DiGeorge Syndrome"
17	TI (digeorge* or di george* or sedlackova* or opitz g-bbb or velocardiofacial or velo-cardiofacial or velo-cardio-facial or shprintzen* or ctaf) OR AB (digeorge* or di george* or sedlackova* or opitz g-bbb or velocardiofacial or velo-cardiofacial or velo-cardio-facial or shprintzen* or ctaf)
18	TI ((deletion or vcf or pharyngeal pouch or thymic aplasia or anomaly face) N1 (syndrome* or disease* or disorder*)) OR AB (((deletion or vcf or pharyngeal pouch or thymic aplasia or anomaly face) N1 (syndrome* or disease* or disorder*))
19	MH "Common Variable Immunodeficiency"

20	TI ((common variable or late onset) N3 (immunodeficienc* or immune deficienc* or immunoglobulin deficienc* or hypogammaglobulin*)) OR AB ((common variable or late onset) N3 (immunodeficienc* or immune deficienc* or immunoglobulin deficienc* or hypogammaglobulin*))
21	TI (acquired hypogammaglobulin*) OR AB (acquired hypogammaglobulin*)
22	TI (cryoglobulin#em*) OR AB (cryoglobulin#em*)
23	TI ((autoimmune or failure*) N3 (polyglandular* or polyendocrin*)) OR AB ((autoimmune or failure*) N3 (polyglandular* or polyendocrin*))
24	MH "Hutchinson-Gilford Progeria Syndrome"
25	TI (progeria or hutchinson-gilford*) OR AB (progeria or hutchinson-gilford*)
26	TI (tyrosin#em*) OR AB (tyrosin#em*)
27	MH "Maple Syrup Urine Disease"
28	TI (maple syrup urine or msud) OR AB (maple syrup urine or msud)
29	TI (branched chain) OR AB (branched chain)
30	TI (bckd N5 (deficienc* or ketoacid* or keto-acid*)) OR AB (bckd N5 (deficienc* or ketoacid* or keto-acid*))
31	TI (hyperleucine-isoleucin*) OR AB (hyperleucine-isoleucin*)
32	MH "Methylmalonic Acid"
33	TI (methylmalonic acid#emi* or methylmalonic aciduri* or methyl malonic acid#emi* or methyl malonic aciduri*) OR AB (methylmalonic acid#emi* or methylmalonic aciduri* or methyl malonic acid#emi* or methyl malonic aciduri*)
34	TI (propionic acid#em* or propionic acidur* or propionyl-CoA carboxylase deficienc* or ketotic glycin#em*) OR AB (propionic acid#em* or propionic acidur* or propionyl-CoA carboxylase deficienc* or ketotic glycin#em*)
35	MH "Adrenoleukodystrophy"
36	TI (adrenoleukodystroph* or x-ald or schilder-addison* or addison-schilder* or adrenomyeloneuropath*) OR AB (adrenoleukodystroph* or x-ald or schilder-addison* or addison-schilder* or adrenomyeloneuropath*)
37	TI ((carnitine palmityltransferase or carnitine palmitoyltransferase or carnitine o-palmityltransferase or carnitine o-palmitoyltransferase) N3 deficienc*) OR AB ((carnitine palmityltransferase or carnitine palmitoyltransferase or carnitine o-palmityltransferase or carnitine o-palmitoyltransferase) N3 deficienc*)
38	MH "Fanconi Syndrome"
39	TI (fanconi* N (syndrome* or disease* or disorder*)) OR AB (fanconi* N (syndrome* or disease* or disorder*))
40	TI (ocular N3 (renal or kidney)) OR AB (ocular N3 (renal or kidney))
41	TI (cystinos* or cystine storage or cystine diathes* or cystine disease*) OR AB (cystinos* or cystine storage or cystine diathes* or cystine disease*)
42	MH "Oculocerebrorenal Syndrome"
43	TI ((lowe or lowes or oculocerebrorenal or cerebrooculorenal or cerebro-oculo-renal) N3 (syndrome* or disease* or disorder*)) OR AB ((lowe or lowes or oculocerebrorenal or cerebrooculorenal or cerebro-oculo-renal) N3 (syndrome* or disease* or disorder*))
44	MH "Metalloproteins/df"
45	MH "Molybdenum/df"
46	TI (molybdenum cofactor deficien* or molybdenum co-factor deficien*) OR AB (molybdenum cofactor deficien* or molybdenum co-factor deficien*)
47	TI ((sulphite* or sulfite*) N3 oxidase deficien*) OR AB ((sulphite* or sulfite*) N3 oxidase deficien*)

48	MH "Argininosuccinic Acid"
49	TI (argininosuccinic acidur* or argininosuccinic acid#emi*) OR AB (argininosuccinic acidur* or argininosuccinic acid#emi*)
50	TI (citrullin#emi* or citrullinuri*) OR AB (citrullin#emi* or citrullinuri*)
51	MH "Amino Acid Metabolism, Inborn Errors"
52	TI (glutaric acid#emi* or glutaric aciduri*) OR AB (glutaric acid#emi* or glutaric aciduri*)
53	TI (glycine encephalopath* or non-ketotic hyperglycin#emi* or nonketotic hyperglycin#emi*) OR AB (glycine encephalopath* or non-ketotic hyperglycin#emi* or nonketotic hyperglycin#emi*)
54	TI (arginin#emi* or arginase deficien* or hyperarginin#emi*) OR AB (arginin#emi* or arginase deficien* or hyperarginin#emi*)
55	MH "Renal Aminoacidurias"
56	TI (aminoaciduri* or aminoacid#emi*) OR AB (arginin#emi* or arginase deficien* or hyperarginin#emi*)
57	MH "glycogen storage disease+"
58	TI (glycogen storage N1 (disease* or syndrome* or disorder*)) OR AB (glycogen storage N1 (disease* or syndrome* or disorder*))
59	TI (pompe* N1 (disease* or syndrome* or disorder*)) OR AB (pompe* N1 (disease* or syndrome* or disorder*))
60	MH "Galactosemia"
61	TI (galactos#emi*) OR AB (galactos#emi*)
62	MH "Pyruvate Dehydrogenase Complex Deficiency Disease"
63	TI (pyruvate dehydrogenase N3 deficien*) OR AB (pyruvate dehydrogenase N3 deficien*)
64	TI (oxalosis and (renal or kidney*)) OR AB (oxalosis and (renal or kidney*))
65	TI (gangliosidos*) OR AB (gangliosidos*)
66	TI (sandhoff* N1 (disease* or syndrome* or disorder*)) OR AB (sandhoff* N1 (disease* or syndrome* or disorder*))
67	TI (tay sach*) OR AB (tay sach*)
68	MH "Mucolipidoses"
69	TI (mucolipidos*) OR AB (mucolipidos*)
70	TI (canavan* leucodystroph* or aspartoacylase deficien* or aminoacylase 2 deficien*) OR AB (canavan* leucodystroph* or aspartoacylase deficien* or aminoacylase 2 deficien*)
71	TI ((canavan* or canavan-van bogaert-bertrand*) N (disease* or syndrome* or disorder*)) OR AB ((canavan* or canavan-van bogaert-bertrand*) N (disease* or syndrome* or disorder*))
72	MH "Gaucher Disease"
73	TI (gaucher* N1 (disease* or syndrome* or disorder*)) OR AB (gaucher* N1 (disease* or syndrome* or disorder*))
74	TI (glucocerebrosidase deficien* or glucosylceramidase deficien*) OR AB (glucocerebrosidase deficien* or glucosylceramidase deficien*)
75	TI (metachromatic leukodystroph* or arylsulfatase A deficien* or metachromic leukodystroph*) OR AB (metachromatic leukodystroph* or arylsulfatase A deficien* or metachromic leukodystroph*)
76	MH "Niemann-Pick Diseases+"
77	TI (niemann-pick* or sphingomyelinase deficien*) OR AB (niemann-pick* or sphingomyelinase deficien*)

78	MH "Sphingolipidoses"
79	TI (sphingolipidos*) OR AB (sphingolipidos*)
80	MH "Fabry Disease"
81	TI (fabry* N1 (disease* or syndrome* or disorder*)) OR AB (fabry* N1 (disease* or syndrome* or disorder*))
82	TI (angiokeratoma corporis diffusum or alpha-galactosidase A deficien*) OR AB (angiokeratoma corporis diffusum or alpha-galactosidase A deficien*)
83	MH"Leukodystrophy, Globoid Cell"
84	TI (krabbe* N1 (disease* or syndrome* or disorder*)) OR AB (krabbe* N1 (disease* or syndrome* or disorder*))
85	TI (globoid cell leukodystroph* or galactosylceramide lipidos* or galactosylcerebrosidase deficien* or galactosylceramidase deficien*) OR AB (globoid cell leukodystroph* or galactosylceramide lipidos* or galactosylcerebrosidase deficien* or galactosylceramidase deficien*)
86	TI (farber* N1 (disease* or syndrome* or disorder*)) OR AB (farber* N1 (disease* or syndrome* or disorder*))
87	TI (farber* lipogranulomatos* or ceramidase deficien* or fibrocytic dysmucopolysaccharidos*) OR AB (farber* lipogranulomatos* or ceramidase deficien* or fibrocytic dysmucopolysaccharidos*)
88	TI (pelizaeus-merzbacher*) OR AB (pelizaeus-merzbacher*)
89	TI (sulfatase deficien* or sulphatase deficien* or mucosulfatidos*) OR AB (sulfatase deficien* or sulphatase deficien* or mucosulfatidos*)
90	TI (austin* N1 (disease* or syndrome* or disorder*)) OR AB (austin* N1 (disease* or syndrome* or disorder*))
91	TI (sulfatidos*) OR AB (sulfatidos*)
92	TI (sea-blue histiocyt*) OR AB (sea-blue histiocyt*)
93	MH "Neuronal Ceroid-Lipofuscinoses"
94	TI (batten* N1 (disease* or syndrome* or disorder*)) OR AB (batten* N1 (disease* or syndrome* or disorder*))
95	TI (neuronal ceroid lipofuscinos* or santavuori-haltia* or jansky-bielschowsky* or bielschowsky-jansky*) OR AB (neuronal ceroid lipofuscinos* or santavuori-haltia* or jansky-bielschowsky* or bielschowsky-jansky*)
96	TI (kuf* N1 (disease* or syndrome* or disorder*)) OR AB (kuf* N1 (disease* or syndrome* or disorder*))
97	TI (spielmeyer vogt*) OR AB (spielmeyer vogt*)
98	MH "Lipid Metabolism, Inborn Errors"
99	TI ((cerebrotendineous or cerebrotendinous or cerebrotendious or cerebral) N3 (xanthomatos* or cholesteros*)) OR AB ((cerebrotendineous or cerebrotendinous or cerebrotendious or cerebral) N3 (xanthomatos* or cholesteros*))
100	TI (bogaert-scherer-epstein*) OR AB (bogaert-scherer-epstein*)
101	TI (wolman* N1 (disease* or syndrome* or disorder*)) OR AB (wolman* N1 (disease* or syndrome* or disorder*))
102	TI (lysosomal acid lipase deficien*) OR AB (lysosomal acid lipase deficien*)
103	MH "Mucopolysaccharidoses+"
104	TI (mucopolysaccharidos*) OR AB (mucopolysaccharidos*)
105	TI (hurler* N2 (syndrome* or disease* or disorder*)) OR AB (hurler* N2 (syndrome* or disease* or disorder*))
106	TI (hunter* N2 (syndrome* or disease* or disorder*)) OR AB (hunter* N2 (syndrome* or disease* or disorder*))

107	TI (MPS1 or MPS2 or MPS3 or MPS4 or MPS5 or MPS6 or MPS7 or MPS-1 or MPS-2 or MPS-3 or MPS-4 or MPS-5 or MPS-6 or MPS-7 or MPSI or MPSII or MPSIII or MPSIV or MPSV or MPSVI or MPSVII or MPS-I or MPS-II or MPS-III or MPS-IV or MPS-V or MPS-VI or MPS-VII) OR AB (MPS1 or MPS2 or MPS3 or MPS4 or MPS5 or MPS6 or MPS7 or MPS-1 or MPS-2 or MPS-3 or MPS-4 or MPS-5 or MPS-6 or MPS-7 or MPSI or MPSII or MPSIII or MPSIV or MPSV or MPSVI or MPSVII or MPS-I or MPS-II or MPS-III or MPS-IV or MPS-V or MPS-VI or MPS-VII)
108	TI (beta glucuronidase deficien* or sly syndrome* or sly disorder* or sly disease*) OR AB (beta glucuronidase deficien* or sly syndrome* or sly disorder* or sly disease*)
109	TI (maroteaux-lamy* or marotaeux-lamy* or polydystrophic dwarfism) OR AB (maroteaux-lamy* or marotaeux-lamy* or polydystrophic dwarfism)
110	TI (morquio* or moriquio* or beta galactosidase deficien*) OR AB (morquio* or moriquio* or beta galactosidase deficien*)
111	TI (sanfilippo* or sanfillipo*) OR AB (sanfilippo* or sanfillipo*)
112	MH "Mucolipidoses"
113	TI (mucolipidos* or pseudo-hurler* or pseudohurler*) OR AB (mucolipidos* or pseudo-hurler* or pseudohurler*)
114	TI ((inclusion-cell or i-cell) N1 (disease* or syndrome* or disorder*)) OR AB ((inclusion-cell or i-cell) N1 (disease* or syndrome* or disorder*))
115	TI (fucosidos* or fucidos*) OR AB (fucosidos* or fucidos*)
116	TI ((cdg or ctg) N1 (disease* or disorder* or syndrome*)) OR AB ((cdg or ctg) N1 (disease* or disorder* or syndrome*))
117	TI (carbohydrate-deficient glycoprotein N (disease* or disorder* or syndrome*)) OR AB (carbohydrate-deficient glycoprotein N (disease* or disorder* or syndrome*))
118	TI (congenital disorder* N3 glycosylation) OR AB (congenital disorder* N3 glycosylation)
119	TI (juvenile gout) OR AB (juvenile gout)
120	MH "Kinky Hair Syndrome"
121	TI (menkes*) OR AB (menkes*)
122	TI ((copper transport or steely hair or kinky hair) N1 (disease* or syndrome* or disorder*)) OR AB ((copper transport or steely hair or kinky hair) N1 (disease* or syndrome* or disorder*))
123	MH "alpha 1-Antitrypsin Deficiency"
124	TI (antitrypsin deficien* or A1AD) OR AB (antitrypsin deficien* or A1AD)
125	TI (AAT deficien* or alpha-1 protease deficien*) OR AB (AAT deficien* or alpha-1 protease deficien*)
126	TI (bisalbumin#emi*) OR AB (bisalbumin#emi*)
127	MH "Lipodystrophy, Congenital Generalized"
128	TI (congenital generali#ed lipodystroph* or berardinelli* or bernardnelli*) OR AB (congenital generali#ed lipodystroph* or berardinelli* or bernardnelli*)
129	MH "Landau-Kleffner Syndrome"
130	TI (landau-kleffner* or infantile acquired aphasia* or acquired epileptic aphasia*) OR AB (landau-kleffner* or infantile acquired aphasia* or acquired epileptic aphasia*)
131	TI (aphasia* N5 convulsive) OR AB (aphasia* N5 convulsive)
132	MH "Rett Syndrome"
133	TI (rett* N (syndrome* or disease* or disorder*)) OR AB (rett* N (syndrome* or disease* or disorder*))
134	TI (cerebroatrophic hyperammon#emi*) OR AB (cerebroatrophic hyperammon#emi*)
135	MH "Huntington’s Disease"

136	TI (huntington*) OR AB (huntington*)
137	MH "Spinocerebellar Ataxias+"
138	TI ((nyhan* or kelley-seegmiller*) N1 (syndrome* or disorder* or disease*)) OR AB ((nyhan* or kelley-seegmiller*) N1 (syndrome* or disorder* or disease*))
139	TI (spinocerebellar ataxia* or ataxia* telangiectasia* or louis-bar* syndrome* or louis-bar* disease* or louis-bar* disorder* or machado-joseph* or joseph* disease* or joseph* disorder* or joseph* syndrome*) OR AB (spinocerebellar ataxia* or ataxia* telangiectasia* or louis-bar* syndrome* or louis-bar* disease* or louis-bar* disorder* or machado-joseph* or joseph* disease* or joseph* disorder* or joseph* syndrome*)
140	MH "Friedreich's Ataxia"
141	TI ((friedreich* or friedrich*) N3 ataxia*) OR AB ((friedreich* or friedrich*) N3 ataxia*)
142	TI (spinocerebellar degenerat*) OR AB (spinocerebellar degenerat*)
143	TI (spinal muscular atroph* or werdnig hoffman*) OR AB (spinal muscular atroph* or werdnig hoffman*)
144	TI (dubowitz* or kugelberg-welander*) OR AB (dubowitz* or kugelberg-welander*)
145	MH "Bulbar Palsy, Progressive"
146	TI (fazio-londe* or faziolonde* or progressive bulbar pals*) OR AB (fazio-londe* or faziolonde* or progressive bulbar pals*)
147	MH "parkinson disease" OR MH "parkinson disease, secondary"
148	TI (parkinson* or hypokinetic rigid syndrome* or hypokinetic rigid disease* or hypokinetic rigid disorder* or paralysis agitan* or shaking pals*) OR AB (parkinson* or hypokinetic rigid syndrome* or hypokinetic rigid disease* or hypokinetic rigid disorder* or paralysis agitan* or shaking pals*)
149	TI (pantothenate kinase-associated neurodegenerat* or PKAN or hallervorden-spatz*) OR AB (pantothenate kinase-associated neurodegenerat* or PKAN or hallervorden-spatz*)
150	TI ((neurodegeneration N3 brain iron accumulation) or NBIA#) OR AB ((neurodegeneration N3 brain iron accumulation) or NBIA#)
151	TI (olivopontocerebellar atroph* or OPCA or olivopontocerebellar degenerat*) OR AB (olivopontocerebellar atroph* or OPCA or olivopontocerebellar degenerat*)
152	TI (multiple system atrophy N5 cerebellar) OR AB (multiple system atrophy N5 cerebellar)
153	TI (alper* N1 (disease* or syndrome* or disorder*)) OR AB (alper* N1 (disease* or syndrome* or disorder*))
154	TI (progressive sclerosing poliodystroph* or progressive infantile poliodystroph*) OR AB (progressive sclerosing poliodystroph* or progressive infantile poliodystroph*)
155	TI (diffuse cerebral sclerosis N5 schilder*) OR AB (diffuse cerebral sclerosis N5 schilder*)
156	MH "Leigh Disease"
157	TI (leigh* N (syndrome* or disease* or disorder*)) OR AB (leigh* N (syndrome* or disease* or disorder*))
158	TI (subacute necrotizing encephalomyelopath* or subacute necrotising encephalomyelopath* or sub-acute necrotizing encephalomyelopath* or sub-acute necrotising encephalomyelopath* or SNEM) OR AB (subacute necrotizing encephalomyelopath* or subacute necrotising encephalomyelopath* or sub-acute necrotizing encephalomyelopath* or sub-acute necrotising encephalomyelopath* or SNEM)

159	TI (aicardi-gouti#res or aicardia-gouti#res) OR AB (aicardi-gouti#res or aicardia-gouti#res)
160	TI (worster-drought* or congenital suprabulbar pares*) OR AB (worster-drought* or congenital suprabulbar pares*)
161	MH "multiple sclerosis" OR MH "multiple sclerosis, chronic progressive" OR MH "multiple sclerosis, relapsing-remitting"
162	TI (multiple sclerosis or disseminated sclerosis or encephalomyelitis disseminata*) OR AB (multiple sclerosis or disseminated sclerosis or encephalomyelitis disseminata*)
163	TI (demyelinating N1 (disease* or syndrome* or disorder*)) OR AB (demyelinating N1 (disease* or syndrome* or disorder*))
164	MH "Epilepsies, Myoclonic+"
165	TI (myoclonic epileps*) OR AB (myoclonic epileps*)
166	TI ((lafora* or merrf* or unverricht-lundborg* or janz*) N1 (disease* or syndrome* or disorder*)) OR AB ((lafora* or merrf* or unverricht-lundborg* or janz*) N1 (disease* or syndrome* or disorder*))
167	TI (lennox-gastaut*) OR AB (lennox-gastaut*)
168	TI (lennox* N1 (syndrome* or disease* or disorder*)) OR AB (lennox* N1 (syndrome* or disease* or disorder*))
169	MH "Spasms, Infantile"
170	TI (west* N1 (syndrome* or disease* or disorder*)) OR AB (west* N1 (syndrome* or disease* or disorder*))
171	TI (epilepsia partialis continua or kojevnikov* or epilepsia partialis continuoa or kozhevnikof*) OR AB (epilepsia partialis continua or kojevnikov* or epilepsia partialis continuoa or kozhevnikof*)
172	MH "Charcot-Marie-Tooth Disease"
173	TI (charcot-marie-tooth* or peroneal muscular atroph*) OR AB (charcot-marie-tooth* or peroneal muscular atroph*)
174	TI (progressive neuropathic muscular atroph* or hereditary peroneal nerve dysfunction* or peroneal neuropath*) OR AB (progressive neuropathic muscular atroph* or hereditary peroneal nerve dysfunction* or peroneal neuropath*)
175	MH "Neuropathies, Hereditary Motor and Sensory"
176	TI (hereditary sensory N3 motor neuropath*) OR AB (hereditary sensory N3 motor neuropath*)
177	TI (hereditary motor N3 sensory neuropath*) OR AB (hereditary motor N3 sensory neuropath*)
178	MH "Peroxisomal Disorders"
179	TI (infantile refsum or infantile phytanic acid storage) OR AB (infantile refsum or infantile phytanic acid storage)
180	TI (congenital myasth#eni*) OR AB (congenital myasth#eni*)
181	MH "Muscular Dystrophy, Duchenne"
182	TI (duchenne muscular dystroph* or dmd) OR AB (duchenne muscular dystroph* or dmd)
183	TI (limb-girdle or erb* muscular dystroph*) OR AB (limb-girdle or erb* muscular dystroph*)
184	TI (sarcoglycanopath* or sarcoglycaopath*) OR AB (sarcoglycanopath* or sarcoglycaopath*)
185	MH "Osteochondrodysplasias"

186	TI (osteochondrodysplas* or schwartz-jampel or chondrodystrophi* myotoni* or myotoni* chondrodystrophi*) OR AB (osteochondrodysplas* or schwartz-jampel or chondrodystrophi* myotoni* or myotoni* chondrodystrophi*)
187	TI (congenita* myotoni* or myotoni* congenita*) OR AB (congenita* myotoni* or myotoni* congenita*)
188	TI (thomsen* N1 (disease* or disorder* or syndrome*)) OR AB (thomsen* N1 (disease* or disorder* or syndrome*))
189	TI ((recessive N3 myotoni*) or becker* myotoni*) OR AB ((recessive N3 myotoni*) or becker* myotoni*)
190	MH "Isaacs' Syndrome"
191	TI (isaac* N1 (syndrome* or disease* or disorder*)) OR AB (isaac* N1 (syndrome* or disease* or disorder*))
192	TI (neuromyotoni*) OR AB (neuromyotoni*)
193	MH "Myotonic Disorders"
194	TI (paramyotoni* congenita* or congenita* paramyotoni*) OR AB (paramyotoni* congenita* or congenita* paramyotoni*)
195	TI (eulenburg* N1 (disease* or syndrome* or disorder*)) OR AB (eulenburg* N1 (disease* or syndrome* or disorder*))
196	TI (myotoni* N1 (disease* or disorder* or syndrome*)) OR AB (myotoni* N1 (disease* or disorder* or syndrome*))
197	TI (pseudomyotoni*) OR AB (pseudomyotoni*)
198	TI (congenital N3 myopath*) OR AB (congenital N3 myopath*)
199	TI (myopathycongenital) OR AB (myopathycongenital)
200	TI ((nemaline or rod) N3 myopath*) OR AB ((nemaline or rod) N3 myopath*)
201	TI ((central core or mini-core or minicore or multicore or multi-core) N1 (disease* or disorder* or syndrome* or myopath*)) OR AB ((central core or mini-core or minicore or multicore or multi-core) N1 (disease* or disorder* or syndrome* or myopath*))
202	TI (fiber type disproportion) OR AB (fiber type disproportion)
203	TI (fibre type disproportion) OR AB (fibre type disproportion)
204	MH "Muscular Dystrophy" AND (TI (congen*) OR AB (congen*))
205	TI (congenital* N5 muscular dystroph*) OR AB (congenital* N5 muscular dystroph*)
206	TI ((centronuclear or myotubular) N1 myopath*) OR AB ((centronuclear or myotubular) N1 myopath*)
207	MH "Mitochondrial Myopathies+"
208	TI (mitochondrial myopath* or mitochondrial encephalomyopath* or chronic progressive external ophthalmopleg*) OR AB (mitochondrial myopath* or mitochondrial encephalomyopath* or chronic progressive external ophthalmopleg*)
209	TI ((melas or kearns-sayre*) N1 (syndrome* or disease* or disorder*)) OR AB ((melas or kearns-sayre*) N1 (syndrome* or disease* or disorder*))
210	MH "Quadriplegia" AND (TI (spastic*) OR AB (spastic*))
211	TI (spastic quadriplegi* or spastic tetraplegi*) OR AB (spastic quadriplegi* or spastic tetraplegi*)
212	MH "Reye's Syndrome"
213	TI (reye* N1 (syndrome* or disease* or disorder*)) OR AB (reye* N1 (syndrome* or disease* or disorder*))
214	TI (multiple pterygium) OR AB (multiple pterygium)
215	MH "Hypertension, Pulmonary" AND (TI (primary*) OR AB (primary*))

216	TI ((primary pulmonary or precapillary pulmonary or idiopathic pulmonary) N1 (hypertension or ht or arterial hypertension)) OR AB ((primary pulmonary or precapillary pulmonary or idiopathic pulmonary) N1 (hypertension or ht or arterial hypertension))
217	TI ((primary bronchopulmonary or precapillary bronchopulmonary or idiopathic bronchopulmonary) N1 (hypertension or ht or arterial hypertension)) OR AB ((primary bronchopulmonary or precapillary bronchopulmonary or idiopathic bronchopulmonary) N1 (hypertension or ht or arterial hypertension))
218	TI ((primary lung or precapillary lung or idiopathic lung) N1 (hypertension or ht or arterial hypertension)) OR AB ((primary lung or precapillary lung or idiopathic lung) N1 (hypertension or ht or arterial hypertension))
219	TI (ipah) OR AB (ipah)
220	MH "Cardiomyopathy, Dilated"
221	TI ((congestive or dilated) N1 cardiomyopath*) OR AB ((congestive or dilated) N1 cardiomyopath*)
222	MH "Cardiomyopathy, Hypertrophic+"
223	TI (hypertrophic N1 cardiomyopath*) OR AB (hypertrophic N1 cardiomyopath*)
224	MH "Cardiomyopathy, Dilated" AND (TI (congen*) OR AB (congen*))
225	TI (congenital N3 cardiomyopath*) OR AB (congenital N3 cardiomyopath*)
226	TI (restrictive cardiomyopath* or obliterative cardiomyopath* or constrictive cardiomyopath*) OR AB (restrictive cardiomyopath* or obliterative cardiomyopath* or constrictive cardiomyopath*)
227	MH "Pulmonary Fibrosis+"
228	TI (pulmonary fibros* or lung fibros* or bronchopulmonary fibros* or fibrosing alveolit* or interstitial pneumonit*) OR AB (pulmonary fibros* or lung fibros* or bronchopulmonary fibros* or fibrosing alveolit* or interstitial pneumonit*)
229	MH "Respiratory Failure"
230	TI (respiratory N1 (failure* or insufficienc*)) OR AB (respiratory N1 (failure* or insufficienc*))
231	MH "Cystic Adenomatoid Malformation of Lung, Congenital"
232	TI ((cystic lung or cystic pulmonary or cystic bronchopulmonary) N1 (disease* or disorder or syndrome*)) OR AB ((cystic lung or cystic pulmonary or cystic bronchopulmonary) N1 (disease* or disorder or syndrome*))
233	TI (bronchogenic cyst* or bronchopulmonary foregut malformation*) OR AB (bronchogenic cyst* or bronchopulmonary foregut malformation*)
234	TI (cystic adenomatoid malformation*) OR AB (cystic adenomatoid malformation*)
235	TI (lobar emphysem*) OR AB (lobar emphysem*)
236	TI (pulmonary sequestration* or bronchopulmonary sequestration* or lung sequestration* or extralobar sequestration* or extra-lobar sequestration* or intralobar sequestration* or intra-lobar sequestration*) OR AB (pulmonary sequestration* or bronchopulmonary sequestration* or lung sequestration* or extralobar sequestration* or extra-lobar sequestration* or intralobar sequestration* or intra-lobar sequestration*)
237	TI (pulmolithias*) OR AB (pulmolithias*)
238	MH "Liver Failure+"
239	TI ((liver# or hepatic) N3 fail*) OR AB ((liver# or hepatic) N3 fail*)
240	MH "Liver Cirrhosis+"
241	TI (cirrhosis N3 liver#) OR AB (cirrhosis N3 liver#)
242	MH "Sinusoidal Obstruction Syndrome"

243	TI ((veno-occlusive or venous occlusive) N1 (disease* or syndrome* or disorder*)) OR AB ((veno-occlusive or venous occlusive) N1 (disease* or syndrome* or disorder*))
244	MH "Exocrine Pancreatic Insufficiency"
245	TI (swachman-diamond or shwachman-bodian or schwachmann-diamond or shwachmann-bodian) OR AB (swachman-diamond or shwachman-bodian or schwachmann-diamond or shwachmann-bodian)
246	MH "Wegener's Granulomatosis"
247	TI (wegener* granulomatos*) OR AB (wegener* granulomatos*)
248	TI (granulomatos* N3 polyangiit*) OR AB (granulomatos* N3 polyangiit*)
249	MH "Osteolysis, Essential"
250	TI (essential osteolys*) OR AB (essential osteolys*)
251	TI ((gorham* or gorham-stout* or vanishing bone or phantom bone) N1 (disease* or syndrome* or disorder)) OR AB ((gorham* or gorham-stout* or vanishing bone or phantom bone) N1 (disease* or syndrome* or disorder))
252	TI ((arc or arthrogryposis renal dysfunction cholestasis) N1 (disease* or syndrome* or disorder)) OR AB ((arc or arthrogryposis renal dysfunction cholestasis) N1 (disease* or syndrome* or disorder))
253	MH "Cerebral Hemorrhage" AND (TI (congen*) OR AB (congen*))
254	MH "Cerebral Hemorrhage" AND TI ((trauma*) OR AB (trauma*))
255	MH "Cerebral Hemorrhage" AND MH "Birth Injuries"
256	TI (cerebral h#emorrhage* and (birth* N3 injur*)) OR AB (cerebral h#emorrhage* and (birth* N3 injur*))
257	MH "Asphyxia Neonatorum"
258	TI (asphyxia neonatorum) OR AB (asphyxia neonatorum)
259	TI ((perinatal* or neonatal* or birth*) N3 asphyxia*) OR AB ((perinatal* or neonatal* or birth*) N3 asphyxia*)
260	MH "Rubella Syndrome, Congenital"
261	TI (congenital rubella) OR AB (congenital rubella)
262	MH "Cytomegalovirus Infections" AND (TI (congen*) OR AB (congen*))
263	TI (congenital N1 (cytomegalovirus* or cmv)) OR AB (congenital N1 (cytomegalovirus* or cmv))
264	MH "Chickenpox" AND (TI congen* or AB congen*)
265	MH "Herpes Zoster+" AND (TI congen* or AB congen*)
266	TI ((congenital or fetal or foetal) N3 (varicella* or chicken pox* or VZV)) Or AB ((congenital or fetal or foetal) N3 (varicella* or chicken pox* or VZV))
267	TI (congenital toxoplasmos*) OR AB (congenital toxoplasmos*)
268	MH "Hypoxia, Brain+"
269	TI ((brain* or cerebral) N3 hypoxi*) OR AB ((brain* or cerebral) N3 hypoxi*)
270	MH "Renal Insufficiency" AND (TI (congen*) OR AB (congen*))
271	MH "Kidney Failure, Acute" AND (TI (congen*) OR AB (congen*))
272	MH "Kidney Failure, Chronic" AND (TI (congen*) OR AB (congen*))
273	MH "Renal Insufficiency, Chronic" AND (TI (congen*) OR AB (congen*))
274	TI (congenital* N3 (kidney failure* or renal failure* or kidney insufficienc* or renal insufficienc*)) OR AB (congenital* N3 (kidney failure* or renal failure* or kidney insufficienc* or renal insufficienc*))
275	TI (congenital* N3 (kidney disease* or renal disease*)) OR AB (congenital* N3 (kidney disease* or renal disease*))
276	MH "Anencephaly"

277	TI (anencephal* or meroanencephal* or craniorachischis*) Or AB (anencephal* or meroanencephal* or craniorachischis*)
278	TI (aprosencephal* N3 open cranium) OR AB (aprosencephal* N3 open cranium)
279	TI (encephalocele* or cranium bifidum) OR AB (encephalocele* or cranium bifidum)
280	TI (dandy-walker*) OR AB (dandy-walker*)
281	MH "Acrocallosal Syndrome"
282	TI (acrocallosal or acro-callosal or acrocolossal or acro colossal) OR AB (acrocallosal or acro-callosal or acrocolossal or acro colossal)
283	MH "Aicardi Syndrome"
284	TI (aicardi* N1 (syndrome* or disease* or disorder*)) OR AB (aicardi* N1 (syndrome* or disease* or disorder*))
285	TI (holoprosencephal* or arhinencephal* or holosprosencephal*) OR AB (holoprosencephal* or arhinencephal* or holosprosencephal*)
286	TI (hydranencephal* or hydrancephal* or hydroanencephal*) OR AB (hydranencephal* or hydrancephal* or hydroanencephal*)
287	MH "Lissencephaly+"
288	MH "Microcephaly"
289	TI (lissencephal* or walker-warburg* or miller-dieker* or norman-robert* or microlissencephal*) OR AB (lissencephal* or walker-warburg* or miller-dieker* or norman-robert* or microlissencephal*)
290	TI ((fukuyama* or muscle-eye-brain) N1 (syndrome* or disease* or disorder*)) OR AB ((fukuyama* or muscle-eye-brain) N1 (syndrome* or disease* or disorder*))
291	MH "Malformations of Cortical Development"
292	TI (microgyria* or microgyrus or micro-gyria* or micro-gyrus) OR AB (microgyria* or microgyrus or micro-gyria* or micro-gyrus)
293	TI (pachygyria* or pachgyria*) OR AB (pachygyria* or pachgyria*)
294	TI (agyria*) OR AB (agyria*)
295	TI ((septo-optic or septooptic) N1 dysplas*) OR AB ((septo-optic or septooptic) N1 dysplas*)
296	TI (de morsier*) OR AB (de morsier*)
297	TI (schizencephal* or schizzencephal*) OR AB (schizencephal* or schizzencephal*)
298	MH "Arnold-Chiari Malformation"
299	TI (chiari* malformation*) OR AB (chiari* malformation*)
300	MH "Truncus Arteriosus, Persistent"
301	TI (truncus or common arterial trunk*) OR AB (truncus or common arterial trunk*)
302	MH "Transposition of Great Arteries"
303	TI ((transposition* or dextrotransposition* or dtransposition* or levotransposition* or ltransposition*) N3 (great arter* or main arter* or aorta* or pulmonary arter* or great vessel* or main vessel*)) OR AB ((transposition* or dextrotransposition* or dtransposition* or levotransposition* or ltransposition*) N3 (great arter* or main arter* or aorta* or pulmonary arter* or great vessel* or main vessel*))
304	TI (dextro-tga or d-tga or levo-tga or l-tga) OR AB (dextro-tga or d-tga or levo-tga or l-tga)
305	TI (double inlet N3 ventricle*) OR AB (double inlet N3 ventricle*)
306	TI (DILV) OR AB (DILV)
307	TI (single ventricle*) OR AB (single ventricle*)
308	MH "Heart Defects, Congenital" AND "Atrial Appendage"
309	TI (isomerism N3 atrial appendage*) OR AB (isomerism N3 atrial appendage*)

310	TI (aspleni* or polyspleni* or poly-spleni*) OR AB (aspleni* or polyspleni* or poly-spleni*)
311	MH "Tetralogy of Fallot"
312	TI (tetralogy N3 fallot*) OR AB (tetralogy N3 fallot*)
313	MH "Eisenmenger Complex"
314	TI (eisenmenger* or tardive cyanos* or eisenmeyer*) OR AB (eisenmenger* or tardive cyanos* or eisenmeyer*)
315	TI (pentalogy N3 fallot*) OR AB (pentalogy N3 fallot*)
316	MH "Pulmonary Atresia"
317	TI ((pulmonary or bronchopulmonary or lung*) N3 atresia*) OR AB ((pulmonary or bronchopulmonary or lung*) N3 atresia*)
318	MH "Tricuspid Atresia"
319	TI ((tricuspid or tri) N3 atresia*) OR AB ((tricuspid or tri) N3 atresia*)
320	MH "Ebstein's Anomaly"
321	TI (ebstein* N (anomal* or malformation*)) OR AB (ebstein* N (anomal* or malformation*))
322	MH "Hypoplastic Left Heart Syndrome"
323	TI (hypoplastic left heart N1 (syndrome* or disease* or disorder*)) OR AB (hypoplastic left heart N1 (syndrome* or disease* or disorder*))
324	TI ((aortic or aorta*) N3 atresia*) OR AB ((aortic or aorta*) N3 atresia*)
325	TI (mitral N3 atresia*) OR AB (mitral N3 atresia*)
326	TI ((absence* or absent*) N3 (aorta* or aortic)) OR AB ((absence* or absent*) N3 (aorta* or aortic))
327	TI (aplas* N3 (aorta* or aortic)) OR AB (aplas* N3 (aorta* or aortic))
328	MH "Aortic Aneurysm+" AND (TI (congen*) OR AB (congen*))
329	TI (((aorta* or aortic) N3 aneurys*) and congenital*) OR AB (((aorta* or aortic) N3 aneurys*) and congenital*)
330	TI (hypoplas* N3 (aorta* or aortic)) OR AB (hypoplas* N3 (aorta* or aortic))
331	TI (convulsion* N3 (aorta* or aortic)) OR AB (convulsion* N3 (aorta* or aortic))
332	TI (persistent right N3 (aorta* or aortic)) OR AB (persistent right N3 (aorta* or aortic))
333	TI ((anomalous pulmonary venous or anamolous pulmonary venous) N1 (connection or drainage or return)) OR AB ((anomalous pulmonary venous or anamolous pulmonary venous) N1 (connection or drainage or return))
334	TI ((absence* or absent*) N3 vena* cava*) OR AB ((absence* or absent*) N3 vena* cava*)
335	TI (persistent left N3 cardinal vein*) OR AB (persistent left N3 cardinal vein*)
336	MH "Scimitar Syndrome"
337	TI ((scimitar* or pulmonary venolobar) N1 (syndrome* or disease* or disorder*)) OR AB ((scimitar* or pulmonary venolobar) N1 (syndrome* or disease* or disorder*))
338	(MH "arteriovenous malformations" OR MH "intracranial arteriovenous malformations") AND (TI (bilateral) OR AB (bilateral))
339	TI ((bilateral AV or bilateral arteriovenous or bilateral arterio-venous) N3 malform*) OR AB ((bilateral AV or bilateral arteriovenous or bilateral arterio-venous) N3 malform*)
340	TI ((trachea* or windpipe* or wind-pipe*) N3 atresia*) OR AB ((trachea* or windpipe* or wind-pipe*) N3 atresia*)

341	TI ((trachea* or laryngotrachea* or glottic or subglottic or sub-glottic) N3 stenosis) OR AB ((trachea* or laryngotrachea* or glottic or subglottic or sub-glottic) N3 stenosis)
342	MH "Bronchopulmonary Dysplasia"
343	TI ((lung* or pulmonary or bronchopulmonary) N3 (hypoplas* or dysplas*)) OR AB ((lung* or pulmonary or bronchopulmonary) N3 (hypoplas* or dysplas*))
344	TI ((absence* or absent*) N3 (esophag* or oesophag* or foodpipe or food-pipe* or gullet*)) OR AB ((absence* or absent*) N3 (esophag* or oesophag* or foodpipe or food-pipe* or gullet*))
345	TI (duoden* N3 atresia*) OR AB (duoden* N3 atresia*)
346	TI ((absence* or absent*) N3 (intestin* or gastrointestin*)) OR AB ((absence* or absent*) N3 (intestin* or gastrointestin*))
347	TI ((intestin* or gastrointestin*) N3 atresia*) OR AB ((intestin* or gastrointestin*) N3 atresia*)
348	TI ((intestin* or gastrointestin*) N3 stenos*) OR AB ((intestin* or gastrointestin*) N3 stenos*)
349	TI (cloaca* N3 (abnor* or malform* or anomal*)) OR AB (cloaca* N3 (abnor* or malform* or anomal*))
350	TI (cloaca* N3 exopthalmo*) OR AB (cloaca* N3 exopthalmo*)
351	MH "Biliary Atresia"
352	TI (biliary N3 atresia*) OR AB (biliary N3 atresia*)
353	TI (extrahepatic ductopen* or extra-hepatic ductopen* or progressive obliterative cholangiopath*) OR AB (extrahepatic ductopen* or extra-hepatic ductopen* or progressive obliterative cholangiopath*)
354	TI (biliary N3 hypoplas*) OR AB (biliary N3 hypoplas*)
355	TI (alagille* N3 atresia*) OR AB (alagille* N3 atresia*)
356	TI ((absence* or absent*) N3 kidney*) OR AB ((absence* or absent*) N3 kidney*)
357	TI (potter* N1 (sequence* or syndrome* or disease* or disorder*)) OR AB (potter* N1 (sequence* or syndrome* or disease* or disorder*))
358	MH "Oligohydramnios"
359	TI (oligohydramn*) OR AB (oligohydramn*)
360	MH "Multicystic Dysplastic Kidney"
361	TI ((kidney* or renal) N3 dysplas*) OR AB ((kidney* or renal) N3 dysplas*)
362	TI ((meckel* or meckelgruber* or gruber*) N1 (syndrome* or disease* or disorder*)) OR AB ((meckel* or meckelgruber* or gruber*) N1 (syndrome* or disease* or disorder*))
363	TI (dysencephalia splanchnocystica*) OR AB (dysencephalia splanchnocystica*)
364	TI (pena-shokeir* or penn-shokeir*) OR AB (pena-shokeir* or penn-shokeir*)
365	TI (larsen* N1 (syndrome* or disease* or disorder*)) OR AB (larsen* N1 (syndrome* or disease* or disorder*))
366	MH "Acrocephalosyndactylia"
367	TI (acrocephalosyndactyl*) OR AB (acrocephalosyndactyl*)
368	TI (pfeiffer* N1 (syndrome* or disease* or syndrome*)) OR AB (pfeiffer* N1 (syndrome* or disease* or syndrome*))
369	MH "Short-Rib Polydactyly Syndrome"
370	TI (short rib#) OR AB (short rib#)
371	TI (saldino-noonan* or majewski* or verma-naumoff* or beemer-langer*) OR AB (saldino-noonan* or majewski* or verma-naumoff* or beemer-langer*)

372	TI (jeune* N1 (syndrome* or disease* or disorder*)) OR AB (jeune* N1 (syndrome* or disease* or disorder*))
373	TI (asphyxiating thoracic dysplas*) OR AB (asphyxiating thoracic dysplas*)
374	TI (chondrodysplasia punctata*) OR AB (chondrodysplasia punctata*)
375	TI ((conradi* or h#nermann* or happle*) N3 (syndrome* or disease* or disorder*)) OR AB ((conradi* or h#nermann* or happle*) N3 (syndrome* or disease* or disorder*))
376	MH "Osteogenesis Imperfecta"
377	TI (osteogenesis imperfecta) OR AB (osteogenesis imperfecta)
378	TI ((brittle bone or lobstein*) N1 (disease* or disorder* or syndrome*)) OR AB ((brittle bone or lobstein*) N1 (disease* or disorder* or syndrome*))
379	MH "Osteochondrodysplasias"
380	TI (spondyloepimetaphyseal or spondyloepiphyseal or spendylo metaphyseal) OR AB (spondyloepimetaphyseal or spondyloepiphyseal or spendylo metaphyseal)
381	MH "Hernia, Umbilical"
382	TI (omphalocele* or omphalocoele* or exomphalos) OR AB (omphalocele* or omphalocoele* or exomphalos)
383	TI (hernia* N3 umbilic*) OR AB (hernia* N3 umbilic*)
384	MH "Gastroschisis"
385	TI (gastroschis*) OR AB (gastroschis*)
386	TI (lamellar* N3 ichthyos*) OR AB (lamellar* N3 ichthyos*)
387	TI ((harlequin* or harloquin*) N3 (ichthyos* or baby or babies or f#etus*)) OR AB ((harlequin* or harloquin*) N3 (ichthyos* or baby or babies or f#etus*))
388	TI (ichthyosis congenita* or ichthyosis fetalis or keratosis diffusa fetalis) OR AB (ichthyosis congenita* or ichthyosis fetalis or keratosis diffusa fetalis)
389	MH "Epidermolysis Bullosa+"
390	TI (epidermolysis bullosa*) OR AB (epidermolysis bullosa*)
391	TI (johanson-blizzard* or johanna-blizzard*) OR AB (johanson-blizzard* or johanna-blizzard*)
392	MH "Xeroderma Pigmentosum"
393	TI (xeroderma pigmentosum) OR AB (xeroderma pigmentosum)
394	MH "Ectodermal Dysplasia"
395	TI (lacrimo-auriculo-dento-digital) OR AB (lacrimo-auriculo-dento-digital)
396	TI (ectodermal dysplas*) OR AB (ectodermal dysplas*)
397	TI ((ladd or eec) N1 (syndrome* or disease* or disorder*)) Or AB ((ladd or eec) N1 (syndrome* or disease* or disorder*))
398	MH "Sturge-Weber Syndrome"
399	TI (sturge-weber or encephalotrigeminal angiomatos*) OR AB (sturge-weber or encephalotrigeminal angiomatos*)
400	MH "Fetal Alcohol Syndrome"
401	TI (f#etal alcohol) OR AB (f#etal alcohol)
402	MH "Pierre Robin Syndrome"
403	TI (pierre robin*) OR AB (pierre robin*)
404	MH "Acrocephalosyndactylia"
405	TI (acrocephalosyndact* or acrocephalopolysyndact*) OR AB (acrocephalosyndact* or acrocephalopolysyndact*)

406	TI ((apert* or crouzon* or saethre-chotzen* or noack* or carpenter* or sakati-nyhan-tisdale* or goodman*) N1 (syndrome* or disorder* or disease*)) OR AB ((apert* or crouzon* or saethre-chotzen* or noack* or carpenter* or sakati-nyhan-tisdale* or goodman*) N1 (syndrome* or disorder* or disease*))
407	TI (fraser* N1 (syndrome* or disease* or disorder*)) OR AB (fraser* N1 (syndrome* or disease* or disorder*))
408	TI (cryptophthalmos) OR AB (cryptophthalmos)
409	TI (cyclopia# or cyclocephal* or synophthalmi*) Or AB (cyclopia# or cyclocephal* or synophthalmi*)
410	MH "Goldenhar Syndrome"
411	TI (goldenhar* or oculo-auriculo-vertebral) OR AB (goldenhar* or oculo-auriculo-vertebral)
412	MH "Mobius Syndrome"
413	TI ((m#bius* or moebius*) N1 (syndrome* or disease* or disorder*)) OR AB ((m#bius* or moebius*) N1 (syndrome* or disease* or disorder*))
414	MH "Orofaciodigital Syndromes"
415	TI (orofaciodigital or oro-facial-digital or oral-facial-digital or papillon-league* or psaume*) OR AB (orofaciodigital or oro-facial-digital or oral-facial-digital or papillon-league* or psaume*)
416	TI (robin* N1 (syndrome* or disorder* or disease*)) OR AB (robin* N1 (syndrome* or disorder* or disease*))
417	TI (freeman-sheldon* or distal arthrogrypos* or craniocarpotarsal dysplas* or craniocarpotarsal dystroph* or canio-carpo-tarsal or windmill-vane-hand* or whistling-face) OR AB (freeman-sheldon* or distal arthrogrypos* or craniocarpotarsal dysplas* or craniocarpotarsal dystroph* or canio-carpo-tarsal or windmill-vane-hand* or whistling-face)
418	MH "De Lange Syndrome"
419	TI ((de lange* or bushy*) N1 (syndrome* or disorder* or disease*)) OR AB ((de lange* or bushy*) N1 (syndrome* or disorder* or disease*))
420	TI (amsterdam dwarfism) OR AB (amsterdam dwarfism)
421	TI (aarskog or faciodigitogenital or facio-digito-genital or facial digital genital or shawl scrotum or faciogenital or facio-genital) OR AB (aarskog or faciodigitogenital or facio-digito-genital or facial digital genital or shawl scrotum or faciogenital or facio-genital)
422	MH "Cockayne Syndrome"
423	TI (cockayne* or neill-dingwall*) OR AB (cockayne* or neill-dingwall*)
424	TI (cerebro-oculo-facio-skeletal or cerebro-oculo-facial-skeletal) OR AB (cerebro-oculo-facio-skeletal or cerebro-oculo-facial-skeletal)
425	TI (dubowitz* N1 (syndrome* or disease* or disorder*)) OR AB (dubowitz* N1 (syndrome* or disease* or disorder*))
426	TI (robinow* or robinhow*) OR AB (robinow* or robinhow*)
427	TI (f#etal face or f#etal facies or f#etal faces or acral dysostos* or mesomelic dwarfism or covesdem*) OR AB (f#etal face or f#etal facies or f#etal faces or acral dysostos* or mesomelic dwarfism or covesdem*)
428	MH "Silver-Russell Syndrome"
429	TI (silver-russell* or russell-silver*) OR AB (silver-russell* or russell-silver*)
430	TI (silver* N1 (syndrome* or disease* or disorder*)) OR AB (silver* N1 (syndrome* or disease* or disorder*))
431	TI ((seckel* or harper*) N1 (syndrome* or disease* or disorder*)) OR AB ((seckel* or harper*) N1 (syndrome* or disease* or disorder*))

432	TI (microcephalic primordial dwarfism or bird-headed dwarf* or virchow-seckel dwarfism) OR AB (microcephalic primordial dwarfism or bird-headed dwarf* or virchow-seckel dwarfism)
433	MH "Smith-Lemli-Opitz Syndrome"
434	TI (smith-lemli-opitz* or dehydrocholesterol reductase deficien*) OR AB (smith-lemli-opitz* or dehydrocholesterol reductase deficien*)
435	MH "Prader-Willi Syndrome"
436	TI (prader-willi* or pradar-willi*) OR AB (prader-willi* or pradar-willi*)
437	MH "Rubinstein-Taybi Syndrome"
438	TI (rubinstein-taybi* or rubenstein-tabyii* or broad thumb-hallux) OR AB (rubinstein-taybi* or rubenstein-tabyii* or broad thumb-hallux)
439	TI ((rubinstein* or rubenstein*) N2 (syndrome* or disease* or disorder*)) OR AB ((rubinstein* or rubenstein*) N2 (syndrome* or disease* or disorder*))
440	MH "Nephritis, Hereditary"
441	TI (alport* N1 (syndrome* or disease* or disorder*)) OR AB (alport* N1 (syndrome* or disease* or disorder*))
442	TI (hereditary nephritis or h#emorrhagic familial nephritis) OR AB (hereditary nephritis or h#emorrhagic familial nephritis)
443	TI (hereditary deafness N3 nephropath*) OR AB (hereditary deafness N3 nephropath*)
444	TI (h#ematuria N3 nephropath* N3 deafness) OR AB (h#ematuria N3 nephropath* N3 deafness)
445	TI (laurence-moon*) OR AB (laurence-moon*)
446	MH "Bardet-Biedl Syndrome"
447	TI (bardet-biedl* or biedl-bardet*) OR AB (bardet-biedl* or biedl-bardet*)
448	MH "Zellweger Syndrome"
449	TI (zellweger*) OR AB (zellweger*)
450	TI ((cerebrohepatorenal or cerebro-hepato-renal) N1 (syndrome* or disease* or disorder*)) OR AB ((cerebrohepatorenal or cerebro-hepato-renal) N1 (syndrome* or disease* or disorder*))
451	TI (edward* N1 (syndrome* or disease* or disorder*)) OR AB (edward* N1 (syndrome* or disease* or disorder*))
452	TI ("trisomy 18") OR AB ("trisomy 18")
453	TI (patau* N1 (syndrome* or disease* or disorder*)) OR AB (patau* N1 (syndrome* or disease* or disorder*))
454	TI ("trisomy 13" or "trisomy D") OR AB ("trisomy 13" or "trisomy D")
455	TI ("trisomy 22") OR AB ("trisomy 22")
456	TI ("trisomy 9") OR AB ("trisomy 9")
457	TI ("trisomy 10") OR AB ("trisomy 10")
458	TI (duplication syndrome*) OR AB (duplication syndrome*)
459	TI (("chromosome 8" or "chr 8") N5 duplicat*) OR AB (("chromosome 8" or "chr 8") N5 duplicat*)
460	TI (("chromosome x" or "chr x") and duplicat*) OR AB (("chromosome x" or "chr x") and duplicat*)
461	TI (chromosom* abnormality N5 duplicat*) OR AB (chromosom* abnormality N5 duplicat*)
462	TI ("tetrasomy 5p") OR AB ("tetrasomy 5p")
463	TI (tetrasomy N3 mosaic*) OR AB (tetrasomy N3 mosaic*)
464	MH "Pallister-Killian Syndrome"

465	TI (delet* N5 short arm N5 "chrom* 4") OR AB (delet* N5 short arm N5 "chrom* 4")
466	TI ((wolf-hirschhorn* or wolff hirschorn* or chromosome deletion dillan* or pitt-rogers-dank* or pitt*) N3 (syndrome* or disease* or disorder*)) OR AB ((wolf-hirschhorn* or wolff hirschorn* or chromosome deletion dillan* or pitt-rogers-dank* or pitt*) N3 (syndrome* or disease* or disorder*))
467	MH "Cri-du-Chat Syndrome"
468	TI ((cri du chat* or crying cat* or 5p or lejeune*) N3 (syndrome* or disease* or disorder*)) OR AB ((cri du chat* or crying cat* or 5p or lejeune*) N3 (syndrome* or disease* or disorder*))
469	TI ((jacobsen* or 11q deletion) N5 (syndrome* or disease* or disorder*)) OR AB ((jacobsen* or 11q deletion) N5 (syndrome* or disease* or disorder*))
470	TI (9p minus or 9p deletion) OR AB (9p minus or 9p deletion)
471	TI (alfi* N1 (syndrome* or disease* or disorder*)) OR AB (alfi* N1 (syndrome* or disease* or disorder*))
472	TI (degouchy* or de gouchy* or degrouchy* or de grouchy*) OR AB (degouchy* or de gouchy* or degrouchy* or de grouchy*)
473	TI (distal 18q) OR AB (distal 18q)
474	MH "Hypoventilation" AND (TI (congen*) Or Ab (congen*))
475	TI (ondine* curse or congenital central hypoventilation or primary alveolar hypoventilation) OR AB (ondine* curse or congenital central hypoventilation or primary alveolar hypoventilation)
476	MH "Graft versus Host Disease" AND (MH "Chronic Disease" or TI (chronic*) OR AB (chronic*))
477	TI (((graft vs host or graft versus host) N1 (disease* or syndrome* or disorder)) and chronic*) OR AB (((graft vs host or graft versus host) N1 (disease* or syndrome* or disorder)) and chronic*)
478	MH "Human Immunodeficiency Virus+"
479	MH "HIV Infections+"
480	TI (HIV or human immunodeficiency virus*) OR AB (HIV or human immunodeficiency virus*)
481	TI (htlv or human t-lymphotropic virus* or human t cell lymphotropic virus*) OR AB (htlv or human t-lymphotropic virus* or human t cell lymphotropic virus*)
482	TI (acquired immune deficiency syndrome* or acquired immunodeficiency syndrome*) OR AB (acquired immune deficiency syndrome* or acquired immunodeficiency syndrome*)
483	TI (AIDS N3 (virus* or infection*)) OR AB (AIDS N3 (virus* or infection*))
484	TI (AIDS N3 (virus* or infection*)) OR AB (AIDS N3 (virus* or infection*))
485	MH "Neoplasms+"
486	TI (cancer* or carcin* or tumor* or tumour* or neoplas* or adenocarcin* or oncol* or malignan*) OR AB (cancer* or carcin* or tumor* or tumour* or neoplas* or adenocarcin* or oncol* or malignan*)
487	MH "Cystic Fibrosis"
488	TI (cystic fibrosis or fibrocystic or fibro-cystic or mucoviscidosis or cf) OR AB (cystic fibrosis or fibrocystic or fibro-cystic or mucoviscidosis or cf)
489	MH "Cerebral Palsy"
490	TI (cerebr* N3 pals*) OR AB (cerebr* N3 pals*)
491	MH "Muscle Spasticity"
492	TI (spasticit*) OR AB (spasticit*)
493	MH "Quadriplegia"

494	TI (spastic* and (quadripleg* or tetrapleg*)) OR AB (spastic* and (quadripleg* or tetrapleg*))
495	MH "Renal Insufficiency+"
496	TI ((kidney* or renal) N3 (failure* or insufficienc*)) OR AB ((kidney* or renal) N3 (failure* or insufficienc*))
497	TI (end stage N3 (kidney or renal)) OR AB (end stage N3 (kidney or renal))
498	TI (("stage 5" or "stage V") N3 (kidney or renal)) OR AB (("stage 5" or "stage V") N3 (kidney or renal))
499	TI (ESRD or ESKD or ESRF or ESKF or CRF or CKF) OR AB (ESRD or ESKD or ESRF or ESKF or CRF or CKF)
500	S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21 OR S22 OR S23 OR S24 OR S25 OR S26 OR S27 OR S28 OR S29 OR S30 OR S31 OR S32 OR S33 OR S34 OR S35 OR S36 OR S37 OR S38 OR S39 OR S40 OR S41 OR S42 OR S43 OR S44 OR S45 OR S46 OR S47 OR S48 OR S49 OR S50 OR S51 OR S52 OR S53 OR S54 OR S55 OR S56 OR S57 OR S58 OR S59 OR S60 OR S61 OR S62 OR S63 OR S64 OR S65 OR S66 OR S67 OR S68 OR S69 OR S70 OR S71 OR S72 OR S73 OR S74 OR S75 OR S76 OR S77 OR S78 OR S79 OR S80 OR S81 OR S82 OR S83 OR S84 OR S85 OR S86 OR S87 OR S88 OR S89 OR S90 OR S91 OR S92 OR S93 OR S94 OR S95 OR S96 OR S97 OR S98 OR S99 OR S100 OR S101 OR S102 OR S103 OR S104 OR S105 OR S106 OR S107 OR S108 OR S109 OR S110 OR S111 OR S112 OR S113 OR S114 OR S115 OR S116 OR S117 OR S118 OR S119 OR S120 OR S121 OR S122 OR S123 OR S124 OR S125 OR S126 OR S127 OR S128 OR S129 OR S130 OR S131 OR S132 OR S133 OR S134 OR S135 OR S136 OR S137 OR S138 OR S139 OR S140 OR S141 OR S142 OR S143 OR S144 OR S145 OR S146 OR S147 OR S148 OR S149 OR S150 OR S151 OR S152 OR S153 OR S154 OR S155 OR S156 OR S157 OR S158 OR S159 OR S160 OR S161 OR S162 OR S163 OR S164 OR S165 OR S166 OR S167 OR S168 OR S169 OR S170 OR S171 OR S172 OR S173 OR S174 OR S175 OR S176 OR S177 OR S178 OR S179 OR S180 OR S181 OR S182 OR S183 OR S184 OR S185 OR S186 OR S187 OR S188 OR S189 OR S190 OR S191 OR S192 OR S193 OR S194 OR S195 OR S196 OR S197 OR S198 OR S199 OR S200 OR S201 OR S202 OR S203 OR S204 OR S205 OR S206 OR S207 OR S208 OR S209 OR S210 OR S211 OR S212 OR S213 OR S214 OR S215 OR S216 OR S217 OR S218 OR S219 OR S220 OR S221 OR S222 OR S223 OR S224 OR S225 OR S226 OR S227 OR S228 OR S229 OR S230 OR S231 OR S232 OR S233 OR S234 OR S235 OR S236 OR S237 OR S238 OR S239 OR S240 OR S241 OR S242 OR S243 OR S244 OR S245 OR S246 OR S247 OR S248 OR S249 OR S250 OR S251 OR S252 OR S253 OR S254 OR S255 OR S256 OR S257 OR S258 OR S259 OR S260 OR S261 OR S262 OR S263 OR S264 OR S265 OR S266 OR S267 OR S268 OR S269 OR S270 OR S271 OR S272 OR S273 OR S274 OR S275 OR S276 OR S277 OR S278 OR S279 OR S280 OR S281 OR S282 OR S283 OR S284 OR S285 OR S286 OR S287 OR S288 OR S289 OR S290 OR S291 OR S292 OR S293 OR S294 OR S295 OR S296 OR S297 OR S298 OR S299 OR S300 OR S301 OR S302 OR S303 OR S304 OR S305 OR S306 OR S307 OR S308 OR S309 OR S310 OR S311 OR S312 OR S313 OR S314 OR S315 OR S316 OR S317 OR S318 OR S319 OR S320 OR S321 OR S322 OR S323 OR S324 OR S325 OR S326 OR S327 OR S328 OR S329 OR S330 OR S331 OR S332 OR S333 OR S334 OR S335 OR S336 OR S337 OR S338 OR S339 OR S340 OR S341 OR S342 OR S343 OR S344 OR S345 OR S346 OR S347 OR S348 OR S349 OR S350 OR S351 OR S352 OR S353 OR S354 OR S355 OR S356 OR S357 OR S358 OR S359 OR S360 OR S361 OR S362 OR S363 OR S364 OR S365 OR S366 OR S367 OR S368 OR S369 OR S370 OR S371 OR S372 OR S373 OR S374 OR S375 OR S376 OR S377 OR S378 OR S379 OR S380 OR S381 OR S382 OR S383 OR S384 OR S385 OR S386 OR S387 OR S388 OR S389 OR

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501	MH "Terminally Ill Patients"
502	MH "Terminal Care"
503	MH "Palliative Care"
504	MH "Hospices" OR MH "Hospice Care"
505	TI (life N2 limit*) OR AB (life N2 limit*)
506	TI (life N2 threaten*) OR AB (life N2 threaten*)
507	TI (end of life) OR AB (end of life)
508	TI (eol) OR AB (eol)
509	TI (terminal* N2 (ill or illness* or condition# or disease# or syndrome* or disorder*)) OR AB (terminal* N2 (ill or illness* or condition# or disease# or syndrome* or disorder*))
510	TI (terminal N2 (care* or caring)) OR AB (terminal N2 (care* or caring))
511	TI (palliat*) Or AB (palliat*)
512	TI (care N2 dying) OR AB (care N2 dying)
513	TI (technology N2 dependent) OR AB (technology N2 dependent)
514	TI (hospice*) OR AB (hospice*)
515	MH "Rare Diseases"
516	MH "Metabolic Diseases"
517	TI (severe N2 (need or needs or illness* or disease# or disabilit* or impairment# or impediment# or condition# or disadvant* or problem# or syndrome# or disorder#)) OR AB (severe N2 (need or needs or illness* or disease# or disabilit* or impairment# or impediment# or condition# or disadvant* or problem# or syndrome# or disorder#))
518	TI (complex N2 (need or needs or illness* or disease# or disabilit* or impairment# or impediment# or condition# or disadvant* or problem# or syndrome# or disorder#)) OR AB (complex N2 (need or needs or illness* or disease# or disabilit* or impairment# or impediment# or condition# or disadvant* or problem# or syndrome# or disorder#))
519	TI (rare N2 (illness* or disease* or disabilit* or impairment* or impediment* or condition# or syndrome# or disorder#)) OR AB (rare N2 (illness* or disease* or disabilit* or impairment* or impediment* or condition# or syndrome# or disorder#))
520	TI (multiple N2 (need or needs or illness* or disease# or disabilit* or impairment# or impediment* or condition# or disadvant* or health or syndrome# or disorder#)) OR AB (multiple N2 (need or needs or illness* or disease# or disabilit* or impairment# or impediment* or condition# or disadvant* or health or syndrome# or disorder#))

521	TI (profound N2 (need or needs or illness* or disease* or disabilit* or impairment* or impediment* or condition# or syndrome# or disorder#)) OR AB (profound N2 (need or needs or illness* or disease* or disabilit* or impairment* or impediment* or condition# or syndrome# or disorder#))
522	TI (intense N2 (need or needs or illness* or disease* or disabilit* or impairment* or impediment* or condition# or syndrome# or disorder#)) OR AB (intense N2 (need or needs or illness* or disease* or disabilit* or impairment* or impediment* or condition# or syndrome# or disorder#))
523	TI (serious N2 (disabilit* or impairment* or impediment* or condition# or disadvant*)) OR AB (serious N2 (disabilit* or impairment* or impediment* or condition# or disadvant*))
524	S502 OR S503 OR S504 OR S505 OR S506 OR S507 OR S508 OR S509 OR S510 OR S511 OR S512 OR S513 OR S514 OR S515 OR S516 OR S517 OR S518 OR S519 OR S520 OR S521 OR S522 OR S523 OR S524
525	S501 OR S525
526	TI ((Young N1 people*) or Youth* or Care leaver* or residential child* or Adolescen* or Young adult* or Young person* or Young men* or Young women* or Teen* or juvenile* or Younger people or Youngster* or Looked after or Child welfare or paediatric* or pediatric* or peadiatric* or Young male* or Young female* or juvenile or children* or child or childhood or (young N1 patient*) or young carer* or minors or puber* or pubescen* or ((secondary or high*) N2 (school* or education))) OR AB ((Young N1 people*) or Youth* or Care leaver* or residential child* or Adolescen* or Young adult* or Young person* or Young men* or Young women* or Teen* or juvenile* or Younger people or Youngster* or Looked after or Child welfare or paediatric* or pediatric* or peadiatric* or Young male* or Young female* or juvenile or children* or child or childhood or (young N1 patient*) or young carer* or minors or puber* or pubescen* or ((secondary or high*) N2 (school* or education)))
527	MH "infant+"
528	MH "Child"
529	S529 NOT S528
530	MH "Child, disabled"
531	MH " Young Adult+"
532	MH "Adolescent, Hospitalized"
533	MH "Child, Institutionalized"
534	MH "Child, Hospitalized"
535	MH "Adolescence+"
536	S527 OR S528 OR S529 OR S530 OR S531 OR S532 OR S533 OR S534 OR S535 OR S536
537	TI ((transition* or transfer* or handoff or handover or hand over) and (Service* or care or clinic* or healthcare or hospital* or center* or centre* or facility or facilities or unit* or department* or institution* or agency or agencies or hospice* or provider* or program* or Coordinat* or Framework* or Managing or Managed or preparedness or Planning or Preparing or Preparation* or Plan* or Protocol* or planned or Support or Supporting or Trajectory or Trajectories or Pathway* or Process or Processes or Readiness or Partnership* or programme* or program* or training or strateg* or Failure* or Barrier* or system#))

538	AB ((transition* or transfer* or handoff or handover or hand over) N3 (Service* or care or clinic* or healthcare or hospital* or center* or centre* or facility or facilities or unit* or department* or institution* or agency or agencies or hospice* or provider* or program* or Coordinat* or Framework* or Managing or Managed or preparedness or Planning or Preparing or Preparation* or Plan* or Protocol* or planned or Support or Supporting or Trajectory or Trajectories or Pathway* or Process or Processes or Readiness or Partnership* or programme* or program* or training or strateg* or Failure* or Barrier* or system#))
539	TI (continu* and (care or healthcare or Support or Supporting or Failure* or Barrier*))
540	AB (continu* N3 (care or healthcare or Support or Supporting or Failure* or Barrier*)
541	MH "Transitional care"
542	MH "continuity of patient care"
543	MH "Patient Care Plans"
544	TI (transition* or transfer* or handoff or handover or hand* over) OR AB (transition* or transfer* or handoff or handover or hand* over)
545	(S543 OR S544) AND S545
546	MH "Transfer, Discharge"
547	S538 OR S539 OR S540 OR S541 OR S542 OR S546 OR S547
548	S526 AND S537 AND S548
549	PT (letter or editorial or comment or news)
550	S549 NOT S550

Social Sciences Citation Index (Web of Science)

Concepts:

1. LLC: lines 1-583
2. Child/young adult: lines 584-595
3. Transition: lines 596-607

1	Creutzfeldt-Jakob Syndrome
2	(creutzfeldt-jakob* or jakob-creutzfeldt* or cjd or spongiform encephalopath*)
4	(subacute sclerosing panencephalit* or sub-acute sclerosing panencephalit* or sspe or subacute sclerosing leukoencephalit* or sub-acute sclerosing leukoencephalit* or van bogaert* leukoencephalit* or measles inclusion body encephalit* or mibe)
5	beta-Thalassemia
6	(beta NEAR/1 (thalass$emi* or thalas$emi*))
7	((thalass$emi* or thalas$emi*) NEAR/1 major)
8	Anemia, Aplastic
9	((hypoplastic or aplastic) NEAR/1 an$emi*)
10	(medullary NEAR/3 hypoplas*)
11	Neutropenia
12	((severe or chronic*) NEAR/3 neutropeni*)
13	immunologic deficiency syndromes or acquired immunodeficiency syndrome
14	(immun* deficiency NEAR/1 (syndrome* or disease* or disorder*))
15	(immunodeficiency NEAR/1 (syndrome* or disease* or disorder*))
16	DiGeorge Syndrome
17	(digeorge* or di george* or sedlackova* or opitz g-bbb or velocardiofacial or velo-cardiofacial or velo-cardio-facial or shprintzen* or ctaf)
18	((deletion or vcf or pharyngeal pouch or thymic aplasia or anomaly face) NEAR/1 (syndrome* or disease* or disorder*))
19	Common Variable Immunodeficiency
20	((common variable or late onset) NEAR/3 (immunodeficienc* or immune deficienc* or immunoglobulin deficienc* or hypogammaglobulin*))
21	acquired hypogammaglobulin*
22	Cryoglobulinemia
23	cryoglobulin$em*
24	Polyendocrinopathies, Autoimmune
25	((autoimmune or failure*) NEAR/3 (polyglandular* or polyendocrin*))
26	Progeria
27	(progeria or hutchinson-gilford*)
28	Tyrosinemias
29	tyrosin$em*
30	Maple Syrup Urine Disease
31	(maple syrup urine or msud)
32	branched chain
33	(bckd NEAR/5 (deficienc* or ketoacid* or keto-acid*))
34	hyperleucine-isoleucin*

35	Methylmalonic Acid
36	(methylmalonic acid$emi* or methylmalonic aciduri* or methyl malonic acid$emi* or methyl malonic aciduri*)
37	Propionic Acidemia
38	(propionic acid$em* or propionic acidur* or propionyl-CoA carboxylase deficienc* or ketotic glycin$em*)
39	Adrenoleukodystrophy
40	(adrenoleukodystroph* or x-ald or schilder-addison* or addison-schilder* or adrenomyeloneuropath*)
41	Carnitine O-Palmitoyltransferase
42	((carnitine palmityltransferase or carnitine palmitoyltransferase or carnitine o-palmityltransferase or carnitine o-palmitoyltransferase) NEAR/3 deficienc*)
43	Fanconi Syndrome
44	(fanconi* NEAR/1 (syndrome* or disease* or disorder*))
45	(ocular NEAR/3 (renal or kidney))
46	Cystinosis
47	(cystinos* or cystine storage or cystine diathes* or cystine disease*)
48	Oculocerebrorenal Syndrome
49	((lowe or lowes or oculocerebrorenal or cerebrooculorenal or cerebro-oculo-renal) NEAR/3 (syndrome* or disease* or disorder*))
50	Metalloproteinsdf
51	Molybdenumdf
52	(molybdenum cofactor deficien* or molybdenum co-factor deficien*)
53	Oxidoreductases Acting on Sulfur Group Donorsdf
54	Sulfite Oxidasedf
55	((sulphite* or sulfite*) NEAR/3 oxidase deficien*)
56	Argininosuccinic Acid
57	(argininosuccinic acid* or argininosuccinic acid$emi*)
58	Citrullinemia
59	(citrullin$emi* or citrullinuri*)
60	Amino Acid Metabolism, Inborn Errors
61	(glutaric acid$emi* or glutaric aciduri*)
62	Hyperglycinemia, Nonketotic
63	(glycine encephalopath* or non-ketotic hyperglycin$emi* or nonketotic hyperglycin$emi*)
64	Hyperargininemia
65	(arginin$emi* or arginase deficien* or hyperarginin$emi*)
66	Renal Aminoacidurias
67	(aminoaciduri* or aminoacid$emi*)
68	glycogen storage disease
69	(glycogen storage NEAR/1 (disease* or syndrome* or disorder*))
70	(pompe* NEAR/1 (disease* or syndrome* or disorder*))
71	Galactosemias
72	galactos$emi*
73	Pyruvate Dehydrogenase Complex Deficiency Disease
74	(pyruvate dehydrogenase NEAR/3 deficien*)
75	(oxalosis and (renal or kidney*))
76	Gangliosidoses
77	gangliosidos*
78	(sandhoff* NEAR/1 (disease* or syndrome* or disorder*))

79	tay sach*
80	Mucolipidoses
81	mucolipidos*
82	Canavan Disease
83	(canavan* leucodystroph* or aspartoacylase deficien* or aminoacylase 2 deficien*)
84	((canavan* or canavan-van bogaert-bertrand*) NEAR/1 (disease* or syndrome* or disorder*))
85	Gaucher Disease
86	(gaucher* NEAR/1 (disease* or syndrome* or disorder*))
87	(glucocerebrosidase deficien* or glucosylceramidase deficien*)
88	Leukodystrophy, Metachromatic
89	(metachromatic leukodystroph* or arylsulfatase A deficien* or metachromic leukodystroph*)
90	Niemann-Pick Diseases
91	(niemann-pick* or sphingomyelinase deficien*)
92	Sphingolipidoses
93	sphingolipidos*
94	Fabry Disease
95	(fabry* NEAR/1 (disease* or syndrome* or disorder*))
96	(angiokeratoma corporis diffusum or alpha-galactosidase A deficien*)
97	Leukodystrophy, Globoid Cell
98	(krabbe* NEAR/1 (disease* or syndrome* or disorder*))
99	(globoid cell leukodystroph* or galactosylceramide lipidos* or galactosylcerebrosidase deficien* or galactosylceramidase deficien*)
100	Farber Lipogranulomatosis
101	(farber* NEAR/1 (disease* or syndrome* or disorder*))
102	(farber* lipogranulomatos* or ceramidase deficien* or fibrocytic dysmucopolysaccharidos*)
103	Pelizaeus-Merzbacher Disease
104	pelizaeus-merzbacher*
105	Sulfatasesdf
106	Multiple Sulfatase Deficiency Disease
107	(sulfatase deficien* or sulphatase deficien* or mucosulfatidos*)
108	(austin* NEAR/1 (disease* or syndrome* or disorder*))
109	sulfatidosis
110	sulfatidos*
111	Sea-Blue Histiocyte Syndrome
112	sea-blue histiocyt*
113	Neuronal Ceroid-Lipofuscinoses
114	(batten* NEAR/1 (disease* or syndrome* or disorder*))
115	(neuronal ceroid lipofuscinos* or santavuori-haltia* or jansky-bielschowsky* or bielschowsky-jansky*)
116	(kuf* NEAR/1 (disease* or syndrome* or disorder*))
117	spielmeyer vogt*
118	Xanthomatosis, Cerebrotendinous
119	((cerebrotendineous or cerebrotendinous or cerebrotendious or cerebral) NEAR/3 (xanthomatos* or cholesteros*))
120	bogaert-scherer-epstein*
121	Wolman Disease

122	(wolman* NEAR/1 (disease* or syndrome* or disorder*))
123	lysosomal acid lipase deficien*
124	Mucopolysaccharidoses
125	mucopolysaccharidos*
126	(hurler* NEAR/2 (syndrome* or disease* or disorder*))
127	(hunter* NEAR/2 (syndrome* or disease* or disorder*))
128	(MPS1 or MPS2 or MPS3 or MPS4 or MPS5 or MPS6 or MPS7 or MPS-1 or MPS-2 or MPS-3 or MPS-4 or MPS-5 or MPS-6 or MPS-7 or MPSI or MPSII or MPSIII or MPSIV or MPSV or MPSVI or MPSVII or MPS-I or MPS-II or MPS-III or MPS-IV or MPS-V or MPS-VI or MPS-VII)
129	(beta glucuronidase deficien* or sly syndrome* or sly disorder* or sly disease*)
130	(maroteaux-lamy* or marotaeux-lamy* or polydystrophic dwarfism)
131	(morquio* or moriquio* or beta galactosidase deficien*)
132	(sanfilippo* or sanfillipo*)
133	Mucolipidoses
134	(mucolipidos* or pseudo-hurler* or pseudohurler*)
135	((inclusion-cell or i-cell) NEAR/1 (disease* or syndrome* or disorder*))
136	Fucosidosis
137	(fucosidos* or fucidos*)
138	"Congenital Disorders of Glycosylation"
139	((cdg or ctg) NEAR/1 (disease* or disorder* or syndrome*))
140	(carbohydrate-deficient glycoprotein NEAR/1 (disease* or disorder* or syndrome*))
141	(congenital disorder* NEAR/3 glycosylation)
142	Lesch-Nyhan Syndrome
143	juvenile gout
144	Menkes Kinky Hair Syndrome
145	menkes*
146	((copper transport or steely hair or kinky hair) NEAR/1 (disease* or syndrome* or disorder*))
147	alpha 1-Antitrypsin Deficiency
148	(antitrypsin deficien* or A1AD)
149	(AAT deficien* or alpha-1 protease deficien*)
150	bisalbumin$emi*
151	Lipodystrophy, Congenital Generalized
152	(congenital generali$ed lipodystroph* or berardinelli* or bernardnelli*)
153	Landau-Kleffner Syndrome
154	(landau-kleffner* or infantile acquired aphasia* or acquired epileptic aphasia*)
155	(aphasia* NEAR/5 convulsive)
156	Rett Syndrome
157	(rett* NEAR/1 (syndrome* or disease* or disorder*))
158	cerebroatrophic hyperammon$emi*
159	Huntington Disease
160	huntington*
161	Spinocerebellar Ataxias
162	((nyhan* or kelley-seegmiller*) NEAR/1 (syndrome* or disorder* or disease*))

163	(spinocerebellar ataxia* or ataxia* telangiectasia* or louis-bar* syndrome* or louis-bar* disease* or louis-bar* disorder* or machado-joseph* or joseph* disease* or joseph* disorder* or joseph* syndrome*)
164	Friedreich Ataxia
165	((friedreich* or friedrich*) NEAR/3 ataxia*)
166	spinocerebellar degenerat*
167	"Spinal Muscular Atrophies of Childhood"
168	(spinal muscular atroph* or werdnig hoffman*)
169	(dubowitz* or kugelberg-welander*)
170	Bulbar Palsy, Progressive
171	(fazio-londe* or faziolonde* or progressive bulbar pals*)
172	parkinson disease or parkinson disease, secondary
173	(parkinson* or hypokinetic rigid syndrome* or hypokinetic rigid disease* or hypokinetic rigid disorder* or paralysis agitan* or shaking pals*)
174	Pantothenate Kinase-Associated Neurodegeneration
175	(pantothenate kinase-associated neurodegenerat* or PKAN or hallervorden-spatz*)
176	((neurodegeneration NEAR/3 brain iron accumulation) or NBIA$)
177	Olivopontocerebellar Atrophies
178	(olivopontocerebellar atroph* or OPCA or olivopontocerebellar degenerat*)
179	(multiple system atrophy NEAR/5 cerebellar)
180	"Diffuse Cerebral Sclerosis of Schilder"
181	(alper* NEAR/1 (disease* or syndrome* or disorder*))
182	(progressive sclerosing poliodystroph* or progressive infantile poliodystroph*)
183	(diffuse cerebral sclerosis NEAR/5 schilder*)
184	Leigh Disease
185	(leigh* NEAR/1 (syndrome* or disease* or disorder*))
186	(subacute necrotizing encephalomyelopath* or subacute necrotising encephalomyelopath* or sub-acute necrotizing encephalomyelopath* or sub-acute necrotising encephalomyelopath* or SNEM)
187	(aicardi-gouti$res or aicardia-gouti$res)
188	(worster-drought* or congenital suprabulbar pares*)
189	multiple sclerosis or multiple sclerosis, chronic progressive or multiple sclerosis, relapsing-remitting
190	(multiple sclerosis or disseminated sclerosis or encephalomyelitis disseminata*)
191	(demyelinating NEAR/1 (disease* or syndrome* or disorder*))
192	Epilepsies, Myoclonic
193	myoclonic epileps*
194	((lafora* or merrf* or unverricht-lundborg* or janz*) NEAR/1 (disease* or syndrome* or disorder*))
195	lennox-gastaut*
196	(lennox* NEAR/1 (syndrome* or disease* or disorder*))
197	Spasms, Infantile
198	(west* NEAR/1 (syndrome* or disease* or disorder*))
199	Epilepsia Partialis Continua
200	(epilepsia partialis continua or kojevnikov* or epilepsia partialis continuoa or kozhevnikof*)
201	Charcot-Marie-Tooth Disease

202	(charcot-marie-tooth* or peroneal muscular atroph*)
203	(progressive neuropathic muscular atroph* or hereditary peroneal nerve dysfunction* or peroneal neuropath*)
204	"Hereditary Sensory and Motor Neuropathy"
205	(hereditary sensory NEAR/3 motor neuropath*)
206	(hereditary motor NEAR/3 sensory neuropath*)
207	Refsum Disease, Infantile
208	Peroxisomal Disorders
209	(infantile refsum or infantile phytanic acid storage)
210	Myasthenic Syndromes, Congenital
211	congenital myasth$eni*
212	Muscular Dystrophy, Duchenne
213	(duchenne muscular dystroph* or dmd)
214	Muscular Dystrophies, Limb-Girdle
215	(limb-girdle or erb* muscular dystroph*)
216	(sarcoglycanopath* or sarcoglycaopath*)
217	Osteochondrodysplasias
218	(osteochondrodysplas* or schwartz-jampel or chondrodystrophi* myotoni* or myotoni* chondrodystrophi*)
219	Myotonia Congenita
220	(congenita* myotoni* or myotoni* congenita*)
221	(thomsen* NEAR/1 (disease* or disorder* or syndrome*))
222	((recessive NEAR/3 myotoni*) or becker* myotoni*)
223	Isaacs Syndrome
224	(isaac* NEAR/1 (syndrome* or disease* or disorder*))
225	neuromyotoni*
226	Myotonic Disorders
227	(paramyotoni* congenita* or congenita* paramyotoni*)
228	(eulenburg* NEAR/1 (disease* or syndrome* or disorder*))
229	(myotoni* NEAR/1 (disease* or disorder* or syndrome*))
230	pseudomyotoni*
231	Myopathies, Structural, Congenital
232	(congenital NEAR/3 myopath*)
233	myopathycongenital
234	((nemaline or rod) NEAR/3 myopath*)
235	((central core or mini-core or minicore or multicore or multi-core) NEAR/1 (disease* or disorder* or syndrome* or myopath*))
236	fiber type disproportion
237	fibre type disproportion
238	Muscular Dystrophiescn
239	(congenital* NEAR/5 muscular dystroph*)
240	((centronuclear or myotubular) NEAR/1 myopath*)
241	Mitochondrial Myopathies
242	(mitochondrial myopath* or mitochondrial encephalomyopath* or chronic progressive external ophthalmopleg*)
243	((melas or kearns-sayre*) NEAR/1 (syndrome* or disease* or disorder*))
244	Quadriplegia and spastic*
245	(spastic quadriplegi* or spastic tetraplegi*)
246	Reye Syndrome
247	(reye* NEAR/1 (syndrome* or disease* or disorder*))

248	multiple pterygium
249	Hypertension, Pulmonary and primary*
250	((primary pulmonary or precapillary pulmonary or idiopathic pulmonary) NEAR/1 (hypertension or ht or arterial hypertension))
251	((primary bronchopulmonary or precapillary bronchopulmonary or idiopathic bronchopulmonary) NEAR/1 (hypertension or ht or arterial hypertension))
252	((primary lung or precapillary lung or idiopathic lung) NEAR/1 (hypertension or ht or arterial hypertension))
253	ipah
254	Cardiomyopathy, Dilated
255	((congestive or dilated) NEAR/1 cardiomyopath*)
256	Cardiomyopathy, Hypertrophic
257	(hypertrophic NEAR/1 cardiomyopath*)
258	Cardiomyopathiescn
259	(congenital NEAR/3 cardiomyopath*)
260	Cardiomyopathy, Restrictive
261	(restrictive cardiomyopath* or obliterative cardiomyopath* or constrictive cardiomyopath*)
262	Pulmonary Fibrosis
263	(pulmonary fibros* or lung fibros* or bronchopulmonary fibros* or fibrosing alveolit* or interstitial pneumonit*)
264	Respiratory Insufficiency
265	(respiratory NEAR/1 (failure* or insufficienc*))
266	"Cystic Adenomatoid Malformation of Lung, Congenital"
267	((cystic lung or cystic pulmonary or cystic bronchopulmonary) NEAR/1 (disease* or disorder or syndrome*))
268	(bronchogenic cyst* or bronchopulmonary foregut malformation*)
269	cystic adenomatoid malformation*
270	lobar emphysem*
271	(pulmonary sequestration* or bronchopulmonary sequestration* or lung sequestration* or extralobar sequestration* or extra-lobar sequestration* or intralobar sequestration* or intra-lobar sequestration*)
272	pulmolithias*
273	Liver Failure
274	((liver*1 or hepatic) NEAR/3 fail*)
275	Liver Cirrhosis
276	(cirrhosis NEAR/3 liver*1)
277	Hepatic Veno-Occlusive Disease
278	((veno-occlusive or venous occlusive) NEAR/1 (disease* or syndrome* or disorder*))
279	Exocrine Pancreatic Insufficiency
280	(swachman-diamond or shwachman-bodian or schwachmann-diamond or shwachmann-bodian)
281	Wegener Granulomatosis
282	wegener* granulomatos*
283	(granulomatos* NEAR/3 polyangiit*)
284	Osteolysis, Essential
285	essential osteolys*
286	((gorham* or gorham-stout* or vanishing bone or phantom bone) NEAR/1 (disease* or syndrome* or disorder))

287	((arc or arthrogryposis renal dysfunction cholestasis) NEAR/1 (disease* or syndrome* or disorder))
288	Cerebral Hemorrhagecn
289	Cerebral Hemorrhage, Traumatic
290	Cerebral Hemorrhage and Birth Injuries
291	(cerebral h$emorrhage* and (birth* NEAR/3 injur*))
292	Asphyxia Neonatorum
293	asphyxia neonatorum
294	((perinatal* or neonatal* or birth*) NEAR/3 asphyxia*)
295	Rubella Syndrome, Congenital
296	congenital rubella
297	Cytomegalovirus Infectionscn
298	(congenital NEAR/1 (cytomegalovirus* or cmv))
299	Chickenpoxcn
300	Herpes Zostercn
301	Herpesvirus 3, Human and congenital*
302	((congenital or fetal or foetal) NEAR/3 (varicella* or chicken pox* or VZV))
303	Toxoplasmosis, Congenital
304	congenital toxoplasmos*
305	Hypoxia, Brain
306	((brain* or cerebral) NEAR/3 hypoxi*)
307	Renal Insufficiencycn
308	Acute Kidney Injurycn
309	Renal Insufficiency, Chroniccn
310	Kidney Failure, Chroniccn
311	(congenital* NEAR/3 (kidney failure* or renal failure* or kidney insufficienc* or renal insufficienc*))
312	(congenital* NEAR/3 (kidney disease* or renal disease*))
313	Anencephaly
314	(anencephal* or meroanencephal* or craniorachischis*)
315	(aprosencephal* NEAR/3 open cranium)
316	Encephalocele
317	(encephalocele* or cranium bifidum)
318	Dandy-Walker Syndrome
319	dandy-walker*
320	Acrocallosal Syndrome
321	(acrocallosal or acro-callosal or acrocolossal or acro colossal)
322	Aicardi Syndrome
323	(aicardi* NEAR/1 (syndrome* or disease* or disorder*))
324	Holoprosencephaly
325	(holoprosencephal* or arhinencephal* or holosprosencephal*)
326	Hydranencephaly
327	(hydranencephal* or hydrancephal* or hydroanencephal*)
328	Lissencephaly
329	Microcephaly
330	(lissencephal* or walker-warburg* or miller-dieker* or norman-robert* or microlissencephal*)
331	((fukuyama* or muscle-eye-brain) NEAR/1 (syndrome* or disease* or disorder*))
332	"Malformations of Cortical Development"

333	(microgyria* or microgyrus or micro-gyria* or micro-gyrus)
334	(pachygyria* or pachgyria*)
335	agyria*
336	Septo-Optic Dysplasia
337	((septo-optic or septooptic) NEAR/1 dysplas*)
338	de morsier*
339	(schizencephal* or schizzencephal*)
340	Arnold-Chiari Malformation
341	chiari* malformation*
342	Truncus Arteriosus, Persistent
343	(truncus or common arterial trunk*)
344	"Transposition of Great Vessels"
345	((transposition* or dextrotransposition* or dtransposition* or levotransposition* or ltransposition*) NEAR/3 (great arter* or main arter* or aorta* or pulmonary arter* or great vessel* or main vessel*))
346	(dextro-tga or d-tga or levo-tga or l-tga)
347	(double inlet NEAR/3 ventricle*)
348	DILV
349	single ventricle*
350	Heart Defects, Congenital and Atrial Appendage
351	(isomerism NEAR/3 atrial appendage*)
352	(aspleni* or polyspleni* or poly-spleni*)
353	"Tetralogy of Fallot"
354	(tetralogy NEAR/3 fallot*)
355	Eisenmenger Complex
356	(eisenmenger* or tardive cyanos* or eisenmeyer*)
357	(pentalogy NEAR/3 fallot*)
358	Pulmonary Atresia
359	((pulmonary or bronchopulmonary or lung*) NEAR/3 atresia*)
360	Tricuspid Atresia
361	((tricuspid or tri) NEAR/3 atresia*)
362	Ebstein Anomaly
363	(ebstein* NEAR/1 (anomal* or malformation*))
364	Hypoplastic Left Heart Syndrome
365	(hypoplastic left heart NEAR/1 (syndrome* or disease* or disorder*))
366	((aortic or aorta*) NEAR/3 atresia*)
367	(mitral NEAR/3 atresia*)
368	((absence* or absent*) NEAR/3 (aorta* or aortic))
369	(aplas* NEAR/3 (aorta* or aortic))
370	Aortic Aneurysmcn
371	(((aorta* or aortic) NEAR/3 aneurys*) and congenital*)
372	(hypoplas* NEAR/3 (aorta* or aortic))
373	(convulsion* NEAR/3 (aorta* or aortic))
374	(persistent right NEAR/3 (aorta* or aortic))
375	((anomalous pulmonary venous or anamolous pulmonary venous) NEAR/1 (connection or drainage or return))
376	((absence* or absent*) NEAR/3 vena* cava*)
377	(persistent left NEAR/3 cardinal vein*)
378	Scimitar Syndrome

379	((scimitar* or pulmonary venolobar) NEAR/1 (syndrome* or disease* or disorder*))
380	(arteriovenous malformations or intracranial arteriovenous malformations) and bilateral
381	((bilateral AV or bilateral arteriovenous or bilateral arterio-venous) NEAR/3 malform*)
382	((trachea* or windpipe* or wind-pipe*) NEAR/3 atresia*)
383	Tracheal Stenosis
384	((trachea* or laryngotrachea* or glottic or subglottic or sub-glottic) NEAR/3 stenosis)
385	Bronchopulmonary Dysplasia
386	((lung* or pulmonary or bronchopulmonary) NEAR/3 (hypoplas* or dysplas*))
387	((absence* or absent*) NEAR/3 (esophag* or oesophag* or foodpipe or food-pipe* or gullet*))
388	Intestinal Atresia
389	(duoden* NEAR/3 atresia*)
390	((absence* or absent*) NEAR/3 (intestin* or gastrointestin*))
391	((intestin* or gastrointestin*) NEAR/3 atresia*)
392	((intestin* or gastrointestin*) NEAR/3 stenos*)
393	(cloaca* NEAR/3 (abnor* or malform* or anomal*))
394	(cloaca* NEAR/3 exopthalmo*)
395	Biliary Atresia
396	(biliary NEAR/3 atresia*)
397	(extrahepatic ductopen* or extra-hepatic ductopen* or progressive obliterative cholangiopath*)
398	(biliary NEAR/3 hypoplas*)
399	(alagille* NEAR/3 atresia*)
400	((absence* or absent*) NEAR/3 kidney*)
401	(potter* NEAR/1 (sequence* or syndrome* or disease* or disorder*))
402	Oligohydramnios
403	oligohydramn*
404	Multicystic Dysplastic Kidney
405	((kidney* or renal) NEAR/3 dysplas*)
406	((meckel* or meckelgruber* or gruber*) NEAR/1 (syndrome* or disease* or disorder*))
407	dysencephalia splanchnocystica*
408	(pena-shokeir* or penn-shokeir*)
409	(larsen* NEAR/1 (syndrome* or disease* or disorder*))
410	Acrocephalosyndactylia
411	acrocephalosyndactyl*
412	(pfeiffer* NEAR/1 (syndrome* or disease* or syndrome*))
413	Short Rib-Polydactyly Syndrome
414	short rib*1
415	(saldino-noonan* or majewski* or verma-naumoff* or beemer-langer*)
416	(jeune* NEAR/1 (syndrome* or disease* or disorder*))
417	asphyxiating thoracic dysplas*
418	Chondrodysplasia Punctata
419	chondrodysplasia punctata*
420	((conradi* or h$nermann* or happle*) NEAR/3 (syndrome* or disease* or disorder*))

421	Osteogenesis Imperfecta
422	osteogenesis imperfecta
423	((brittle bone or lobstein*) NEAR/1 (disease* or disorder* or syndrome*))
424	Osteochondrodysplasias
425	(spondyloepimetaphyseal or spondyloepiphyseal or spendylo metaphyseal)
426	Hernia, Umbilical
427	(omphalocele* or omphalocoele* or exomphalos)
428	(hernia* NEAR/3 umbilic*)
429	Gastroschisis
430	gastroschis*
431	Ichthyosis, Lamellar
432	(lamellar* NEAR/3 ichthyos*)
433	((harlequin* or harloquin*) NEAR/3 (ichthyos* or baby or babies or f$etus*))
434	(ichthyosis congenita* or ichthyosis fetalis or keratosis diffusa fetalis)
435	Epidermolysis Bullosa
436	epidermolysis bullosa*
437	(johanson-blizzard* or johanna-blizzard*)
438	Xeroderma Pigmentosum
439	xeroderma pigmentosum
440	Ectodermal Dysplasia
441	lacrimo-auriculo-dento-digital
442	ectodermal dysplas*
443	((ladd or eec) NEAR/1 (syndrome* or disease* or disorder*))
444	Sturge-Weber Syndrome
445	(sturge-weber or encephalotrigeminal angiomatos*)
446	Fetal Alcohol Spectrum Disorders
447	f$etal alcohol
448	Pierre Robin Syndrome
449	pierre robin*
450	Acrocephalosyndactylia
451	(acrocephalosyndact* or acrocephalopolysyndact*)
452	((apert* or crouzon* or saethre-chotzen* or noack* or carpenter* or sakati-nyhan-tisdale* or goodman*) NEAR/1 (syndrome* or disorder* or disease*))
453	Fraser Syndrome
454	(fraser* NEAR/1 (syndrome* or disease* or disorder*))
455	cryptophthalmos
456	(cyclopia*1 or cyclocephal* or synophthalmi*)
457	Goldenhar Syndrome
458	(goldenhar* or oculo-auriculo-vertebral)
459	Mobius Syndrome
460	((m$bius* or moebius*) NEAR/1 (syndrome* or disease* or disorder*))
461	Orofaciodigital Syndromes
462	(orofaciodigital or oro-facial-digital or oral-facial-digital or papillon-league* or psaume*)
463	(robin* NEAR/1 (syndrome* or disorder* or disease*))
464	(freeman-sheldon* or distal arthrogrypos* or craniocarpotarsal dysplas* or craniocarpotarsal dystroph* or canio-carpo-tarsal or windmill-vane-hand* or whistling-face)
465	De Lange Syndrome
466	((de lange* or bushy*) NEAR/1 (syndrome* or disorder* or disease*))

467	amsterdam dwarfism
468	(aarskog or faciodigitogenital or facio-digito-genital or facial digital genital or shawl scrotum or faciogenital or facio-genital)
469	Cockayne Syndrome
470	(cockayne* or neill-dingwall*)
471	(cerebro-oculo-facio-skeletal or cerebro-oculo-facial-skeletal)
472	(dubowitz* NEAR/1 (syndrome* or disease* or disorder*))
473	(robinow* or robinhow*)
474	(f$etal face or f$etal facies or f$etal faces or acral dysostos* or mesomelic dwarfism or covesdem*)
475	Silver-Russell Syndrome
476	(silver-russell* or russell-silver*)
477	(silver* NEAR/1 (syndrome* or disease* or disorder*))
478	((seckel* or harper*) NEAR/1 (syndrome* or disease* or disorder*))
479	(microcephalic primordial dwarfism or bird-headed dwarf* or virchow-seckel dwarfism)
480	Smith-Lemli-Opitz Syndrome
481	(smith-lemli-opitz* or dehydrocholesterol reductase deficien*)
482	Prader-Willi Syndrome
483	(prader-willi* or pradar-willi*)
484	Rubinstein-Taybi Syndrome
485	(rubinstein-taybi* or rubenstein-tabyii* or broad thumb-hallux)
486	((rubinstein* or rubenstein*) NEAR/2 (syndrome* or disease* or disorder*))
487	Nephritis, Hereditary
488	(alport* NEAR/1 (syndrome* or disease* or disorder*))
489	(hereditary nephritis or h$emorrhagic familial nephritis)
490	(hereditary deafness NEAR/3 nephropath*)
491	(h$ematuria NEAR/3 nephropath* NEAR/3 deafness)
492	Laurence-Moon Syndrome
493	laurence-moon*
494	Bardet-Biedl Syndrome
495	(bardet-biedl* or biedl-bardet*)
496	Zellweger Syndrome
497	zellweger*
498	((cerebrohepatorenal or cerebro-hepato-renal) NEAR/1 (syndrome* or disease* or disorder*))
499	(edward* NEAR/1 (syndrome* or disease* or disorder*))
500	"trisomy 18"
501	(patau* NEAR/1 (syndrome* or disease* or disorder*))
502	("trisomy 13" or "trisomy D")
503	"trisomy 22"
504	"trisomy 9"
505	"trisomy 10"
506	duplication syndrome*
507	(("chromosome 8" or "chr 8") NEAR/5 duplicat*)
508	Chromosome Duplication
509	X Chromosomeab
510	X Chromosome and duplicat*
511	(("chromosome x" or "chr x") and duplicat*)
512	(chromosom* abnormality NEAR/5 duplicat*)

513	"tetrasomy 5p"
514	(tetrasomy NEAR/3 mosaic*)
515	Chromosomes, Human, Pair 5 and Mosaicism
516	Tetrasomy
517	Trisomy and (chromosomes, human, pair 9 or chromosomes, human, pair 10 or chromosomes, human, pair 13 or Chromosomes, Human, Pair 18 or chromosomes, human, pair 22)
518	Chromosome Deletion and Chromosomes, Human, Pair 4
519	(delet* NEAR/5 short arm NEAR/5 "chrom* 4")
520	Wolf-Hirschhorn Syndrome
521	((wolf-hirschhorn* or wolff hirschorn* or chromosome deletion dillan* or pitt-rogers-dank* or pitt*) NEAR/3 (syndrome* or disease* or disorder*))
522	Cri-du-Chat Syndrome
523	((cri du chat* or crying cat* or 5p or lejeune*) NEAR/3 (syndrome* or disease* or disorder*))
524	Jacobsen Distal 11q Deletion Syndrome
525	((jacobsen* or 11q deletion) NEAR/5 (syndrome* or disease* or disorder*))
526	Monosomy and Chromosomes, Human, Pair 9
527	(9p minus or 9p deletion)
528	(alfi* NEAR/1 (syndrome* or disease* or disorder*))
529	(degouchy* or de gouchy* or degrouchy* or de grouchy*)
530	distal 18q
531	Hypoventilationcn
532	(ondine* curse or congenital central hypoventilation or primary alveolar hypoventilation)
533	Graft vs Host Disease and (Chronic Disease or chronic*)
534	(((graft vs host or graft versus host) NEAR/1 (disease* or syndrome* or disorder)) and chronic*)
535	or1-534
536	Terminally Ill
537	Terminal Care
538	Palliative Care
539	Hospices or Hospice Care
540	(life NEAR/2 limit*)
541	(life NEAR/2 threaten*)
542	end of life
543	eol
544	(terminal* NEAR/2 (ill or illness* or condition*1 or disease*1 or syndrome* or disorder*))
545	(terminal NEAR/2 (care* or caring))
546	palliat*
547	(care NEAR/2 dying)
548	(technology NEAR/2 dependent)
549	hospice*
550	Rare Diseases
551	Metabolic Diseases
552	(severe NEAR/2 (need or needs or illness* or disease*1 or disabilit* or impairment*1 or impediment*1 or condition*1 or disadvant* or problem*1 or syndrome*1 or disorder*1))

553	(complex NEAR/2 (need or needs or illness* or disease*1 or disabilit* or impairment*1 or impediment*1 or condition*1 or disadvant* or problem*1 or syndrome*1 or disorder*1))
554	(rare NEAR/2 (illness* or disease* or disabilit* or impairment* or impediment* or condition*1 or syndrome*1 or disorder*1))
555	(multiple NEAR/2 (need or needs or illness* or disease*1 or disabilit* or impairment*1 or impediment* or condition*1 or disadvant* or health or syndrome*1 or disorder*1))
556	(profound NEAR/2 (need or needs or illness* or disease* or disabilit* or impairment* or impediment* or condition*1 or syndrome*1 or disorder*1))
557	(intense NEAR/2 (need or needs or illness* or disease* or disabilit* or impairment* or impediment* or condition*1 or syndrome*1 or disorder*1))
558	(serious NEAR/2 (disabilit* or impairment* or impediment* or condition*1 or disadvant*))
559	or536-558
560	HIV
561	HIV Infections
562	(HIV or human immunodeficiency virus*)
563	(htlv or human t-lymphotropic virus* or human t cell lymphotropic virus*)
564	(acquired immune deficiency syndrome* or acquired immunodeficiency syndrome*)
565	(AIDS NEAR/3 (virus* or infection*))
566	(AIDS NEAR/1 (related or associated))
567	Neoplasms
568	(cancer* or carcin* or tumor* or tumour* or neoplas* or adenocarcin* or oncol* or malignan*)
569	Cystic Fibrosis
570	(cystic fibrosis or fibrocystic or fibro-cystic or mucoviscidosis or cf)
571	Cerebral Palsy
572	(cerebr* NEAR/3 pals*)
573	Muscle Spasticity
574	spasticit*
575	Quadriplegia
576	(spastic* and (quadripleg* or tetrapleg*))
577	Renal Insufficiency
578	((kidney* or renal) NEAR/3 (failure* or insufficienc*))
579	(end stage NEAR/3 (kidney or renal))
580	(("stage 5" or "stage V") NEAR/3 (kidney or renal))
581	(ESRD or ESKD or ESRF or ESKF or CRF or CKF)
582	or560-581
583	535 or 559 or 582
584	((Young NEAR/1 people*) or Youth* or Care leaver* or residential child* or Adolescen* or Young adult* or Young person* or Young men* or Young women* or Teen* or juvenile* or Younger people or Youngster* or Looked after or Child welfare or paediatric* or pediatric* or peadiatric* or Young male* or Young female* or juvenile or children* or child or childhood or (young NEAR/1 patient*) or young carer* or minors or puber* or pubescen* or ((secondary or high*) NEAR/2 (school* or education)))
585	infant
586	Child

587	586 not 585
588	Disabled children
589	Young Adult
590	Adolescent, Hospitalized
591	Adolescent, Institutionalized
592	Child, Institutionalized
593	Child, Hospitalized
594	Adolescent
595	or584,587-594
596	((transition* or transfer* or handoff or handover or hand over) and (Service* or care or clinic* or healthcare or hospital* or center* or centre* or facility or facilities or unit* or department* or institution* or agency or agencies or hospice* or provider* or program* or Coordinat* or Framework* or Managing or Managed or preparedness or Planning or Preparing or Preparation* or Plan* or Protocol* or planned or Support or Supporting or Trajectory or Trajectories or Pathway* or Process or Processes or Readiness or Partnership* or programme* or program* or training or strateg* or Failure* or Barrier* or system$))
597	((transition* or transfer* or handoff or handover or hand over) NEAR/3 (Service* or care or clinic* or healthcare or hospital* or center* or centre* or facility or facilities or unit* or department* or institution* or agency or agencies or hospice* or provider* or program* or Coordinat* or Framework* or Managing or Managed or preparedness or Planning or Preparing or Preparation* or Plan* or Protocol* or planned or Support or Supporting or Trajectory or Trajectories or Pathway* or Process or Processes or Readiness or Partnership* or programme* or program* or training or strateg* or Failure* or Barrier* or system$))
598	(continu* and (care or healthcare or Support or Supporting or Failure* or Barrier*))
599	(continu* NEAR/3 (care or healthcare or Support or Supporting or Failure* or Barrier*))
600	transition to adult care
601	continuity of patient care
602	patient handoff
603	Patient Care Planning
604	Patient transfer
605	(transition* or transfer* or handoff or handover or hand* over)
606	(601 or 603) and 605
607	or596-600,602,604,606
608	583 and 595 and 607
609	(letter or editorial or comment or news).pt.
610	animals not humans
611	608 not (609 or 610)
612	limit 611 to (english language and yr="1990 -Current")

A2.1.3 Data extraction form

Study ID: from Covidence
Paper title:
Authors:
Date of publication:
Type of publication: e.g. peer reviewed journal, conference abstract
Publisher: e.g. journal
Extractor: DR or SJ
Date of extraction:

Item	Description	Page number
Study setting and data		
Country	Must be OECD for inclusion	
Setting	e.g. hospital, transition clinic	
Overall aim	e.g. looking at care through transition, looking at care variations by age	
Date of data collection		
Data sources	e.g. survey, case note review, routine medical records	
Study design	e.g. cohort, quasi-experimental, trial	
Interventions	If any – e.g. a transition programme	
Participants		
Number of participants		
Number pre-transition		
Number post-transition		
Diagnoses	e.g. LLC in general, heart conditions, oncology	
Age range		
Transition age	If an explicit pre-transition group identified, age or age range of transition, if not note no explicit grouping	
Genders	Male, female, both (with balance)	
Ethnic groups	Groups included, split if available	
Deprivation categories	Groups included, split if available	
Outcomes and analyses		
Outcome measured	e.g. number of inpatient admissions	
Groups compared, comparision period	detail on the comparison groups - e.g. range of ages in groups compared; length of time compared	
Type of measurement	e.g. mean difference, odds-ratios, risk ratios	
Subgroups	e.g. by ethnic group, diagnosis, sex – record results by subgroup below	
Statistical methods/tests	e.g. regression type, t-tests etc	
Results		
Measured changes in care	e.g. point estimates, 95%CI, p-values of observed changes	
Other relevant measures	Any other relevant results	
Missing data	% missing, imputation?	

Summary		
Study conclusions	e.g. change or no change at transition	
Limitations	Any obvious limitations/conflicts of interest	

Newcastle Ottawa Scale	Item	Score
Selection	Representativeness of exposed cohort	
	Selection on non-exposed cohort	
	Exposure ascertainment	
	Demonstration outcome not present at start of study	N/A
Comparability	Comparability of cohorts	
Outcome	Assessment of outcome	
	Follow-up long enough	
	Adequacy of follow-up	
Overall	**Total score**	

A2.1.4 Modified Newcastle-Ottawa Scale

Selection

1) Representativeness of the transitioned group (in cross section) or the cohort after transition is

Score 1 if:

a) truly representative of the average child with the given condition in the community

or

b) somewhat representative of the average child with the given condition in the community

Score 0 if

c) selected group of users eg nurses, volunteers

or

d) no description of the derivation of the cohort

2) Selection of the non exposed group

Score 1 if

a) drawn from the same community as the exposed group (or if a single cohort is followed through transition)

Score 0 if

b) drawn from a different source

or

c) no description of the derivation of the non exposed cohort

3) Ascertainment of transition

Score 1 if

a) secure record (eg clinic or medical records) or age based if evidence provided that transition definitively happens at a set age

or

b) structured interview

Score 0 if

c) written self report/based on simple age cut off when not all transitioned at that age (or evidence not provided)

or

d) no description

4) Demonstration that outcome of interest was not present at start of study

Not relevant for this review. No score given.

Comparability

1) Comparability of cohorts on the basis of the design or analysis

Score 1 if

a) study controls for demographic differences including age (cross-sectional study) or age (cohort study)

Score an additional 1 if

b) study controls for disease severity/progression in the two groups or matching was used

Outcome

1) Assessment of outcome

Score 1 if

a) independent blind assessment

or

b) record linkage, e.g. medical/clinic/administrative records

Score 0 if

c) self report

or

d) no description

2) Was follow-up long enough for outcomes to occur

Score 1 if

a) yes (at least 1 year for both pre and post transition)

Score 0 if

b) no (less than 1 year for both pre and post transition)

3) Adequacy of follow up of cohorts

Score 1 if

a) complete follow up - all subjects accounted for

or

b) subjects lost to follow up unlikely to introduce bias - small number lost (≤10%) or description provided of those lost justifying lack of bias due to loss to follow-up

Score 0 if

c) follow up rate < 90% and no description of those lost

or

d) no statement

A2.2 Supplementary materials for paper 4: Adult healthcare is associated with more emergency healthcare for young people with life-limiting conditions

A2.2.1 Supplementary material S1: Coding frameworks used to assign individuals to condition groups

Table S1: ICD-10 and Read codes used to identify young people with diabetes. ICD-10 codes are shown as 3 digits and include all 4 digit codes beginning with these 3 digits.

ICD-10	Read
E10, E11, E12, E13, E14	Cyu2.00, C10..00, C10C.00, C10D.00, C10H.00, C102z00, C101z00, C103z00, C106z00, C100z00, C105z00, C10yz00, C107z00, C10zz00, C107.11, C102.00, C101.00, C103.00, C104z00, C106.12, C10<0.01, C105.00, C10y.00, C107.00, C106.13, C104.00, C10z.00, C107000, C105000, C10z000, C100000, C102000, C101000, C103000, C104000, C106000, C10y000, 66AI.00, 66AJ.00, 66AJz00, 66A5.00, 66o6.00, 66AV.00, 66o2.00, 66A4.00, 66o5.00, 66As.00, C108.11, C108J00, C108G00, C108900, C10E912, C100011, C108.00, C10E.12, C108800, C10E812, C108H00, C108F00, C10EF12, C108600, C10E612, C108E00, C10EE12, C108B00, C10E312, C108300, C108D00, C10ED12, C108C00, C10EC12, C108700, C10E712, C108500, C10E512, C109J11, C10FJ00, C109J00, C10FJ11, C108200, C10E212, C108100, C10E112, C108000, C10E012, C108A00, C10EA12, C10M.00, K01x100, C109E00, C109H00, C100112, C109700, C109G00, C109500, C109D00, C109A00, C109C00, C109B00, C109400, C109F00, C109300, C109200, C109100, C109000, C109900, C10N.00, C10N000, C10G.00, C10G000, C10E.00, C108.12, C10E800, C108812, C10P011, C10E900, C108912, C10EH00, C10EF00, C108F12, C10EP00, C10E600, C10EQ00, C10EE00, C108E12, C10EM00, C10EN00, C10EB00, C10E300, C10ED00, C10E200, C108212, C108J12, C10EJ00, C10E100, C108112, C10EG00, C10EL00, C10EK00, C10EC00, C108012, C10E000, C10E700, C108712, C108512, C10EA00, C108A12, C10F.00, C109.12, C10F700, C109712, C10P111, C109G12, C10FG00, C109E12, C10FE00, C10FQ00, C10F500, C109512, C10FR00, C10FD00, C109D12, C10FN00, C10FP00, C10FA00, C10F300, C109312, C10FC00, C109C12, C10F200, C109212, C10FH00, C109H12, C10F100, C109112, C10FF00, C109F12, C10FM00, C10FL00, C10FB00, C109B12, C10F000, C10F600, C109612, C10F400, C109412, C10F900, C109912, C108.13, C108811, C10E811, C10P000, C108911, C10E911, C108H11, C108F11, C10EP11, C10E611, C10EQ11, C108E11, C10EM11, C10EN11, C108B11, C10E311, C108311, C108D11, C108211, C108J11, C10E111, C10EL11, C10EC11, C108011, C10E011, C108711, C10E711, C108511, C10E511, C10EA11, C108A11, 66At000, C109.13, C10F.11, C109711, C10F711, C10P100, C109G11, C10FG11, C109E11, C10FE11, C10FQ11, C109511, C10F511, C109D11, C10FD11, C10FN11, C10FP11, C109A11, C10FA11, C10F311, C109C11, C10FC11, C109211, C10F211, C109H11, C10FH11, C109111, C10F111, C109F11, C10FF11, C10FL11, C109B11, C10FB11, C109011, C10F011, C10F611, C109611, C109411, C10F411, C10F911, C109911, C108z00

A2.2.2 Supplementary material S2: Classification of records as adult or paediatric

Table S2: Classification of treatment and consultant main specialties as paediatric or adult.

Treatment Specialty	Paediatric	Adult	Unclassified
100 = General Surgery		Y	
101 = Urology		Y	
102 = Transplantation Surgery (Includes Renal And Liver Transplants, Excludes Cardiothoracic Transplantation)		Y	
103 = Breast Surgery (Includes Suspected Neoplasms, Cysts Etc, Does Not Include Cosmetic Surgery)		Y	
104 = Colorectal Surgery (Surgical Treatment Of Disorders Of The Lower Intestine - Colon, Anus And Rectum)		Y	
105 = Hepatobiliary & Pancreatic Surgery (Includes Liver Surgery But Excludes Liver Transplantation See Transplantation Surgery)		Y	
106 = Upper Gastrointestinal Surgery		Y	
107 = Vascular Surgery		Y	
108 = Spinal Surgery Service (From April 2013)		Y	
110 = Trauma & Orthopaedics			Y
120 = Ear, Nose And Throat (ENT)		Y	
130 = Ophthalmology		Y	
140 = Oral Surgery		Y	
141 = Restorative Dentistry (Endodontics, Periodontics And Prosthodontics)		Y	
142 = Paediatric Dentistry	Y		
143 = Orthodontics			Y
144 = Maxillo-Facial Surgery		Y	
150 = Neurosurgery		Y	
160 = Plastic Surgery		Y	
161 = Burns Care (Recognised Specialist Services Only - Includes 'Outreach' Facilities)		Y	
170 = Cardiothoracic Surgery (Where There Are No Separate Services For Cardiac And Thoracic Surgery)		Y	
171 = Paediatric Surgery	Y		
172 = Cardiac Surgery		Y	
173 = Thoracic Surgery		Y	
174 = Cardiothoracic Transplantation (Recognised Specialist Services Only - Includes 'Outreach' Facilities)		Y	
180 = Emergency (EMERGENCY DEPARTMENT)			Y
190 = Anaesthetics		Y	
191 = Pain Management (Complex Pain Disorders Requiring Diagnosis And Treatment By A Specialist Multi-Professional Team)		Y	
192 = Critical Care Medicine (Also Known As Intensive Care Medicine)		Y	
199 = Non-Uk Provider - Specialty Function Not Known, Treatment Mainly Surgical		Y	
211 = Paediatric Urology (From 2006-07)	Y		

212 = Paediatric Transplantation Surgery (From 2006-07)	Y		
213 = Paediatric Gastrointestinal Surgery (From 2006-07)	Y		
214 = Paediatric Trauma And Orthopaedics (From 2006-07)	Y		
215 = Paediatric Ear Nose And Throat (From 2006-07)	Y		
216 = Paediatric Ophthalmology (From 2006-07)	Y		
217 = Paediatric Maxillo-Facial Surgery (From 2006-07)	Y		
218 = Paediatric Neurosurgery (From 2006-07)	Y		
219 = Paediatric Plastic Surgery (From 2006-07)	Y		
220 = Paediatric Burns Care (From 2006-07)	Y		
221 = Paediatric Cardiac Surgery (From 2006-07)	Y		
222 = Paediatric Thoracic Surgery (From 2006-07)	Y		
223 = Paediatric Epilepsy (From April 2013)	Y		
241 = Paediatric Pain Management (From 2006-07)	Y		
242 = Paediatric Intensive Care (From 2006-07)	Y		
251 = Paediatric Gastroenterology (From 2006-07)	Y		
252 = Paediatric Endocrinology (From 2006-07)	Y		
253 = Paediatric Clinical Haetology (From 2006-07)	Y		
254 = Paediatric Audiological Medicine (From 2006-07)	Y		
255 = Paediatric Clinical Immunology And Allergy (From 2006-07)	Y		
256 = Paediatric Infectious Diseases (From 2006-07)	Y		
257 = Paediatric Dermatology (From 2006-07)	Y		
258 = Paediatric Respiratory Medicine (From 2006-07)	Y		
259 = Paediatric Nephrology (From 2006-07)	Y		
260 = Paediatric Medical Oncology (From 2006-07)	Y		
261 = Paediatric Metabolic Disease (From 2006-07)	Y		
262 = Paediatric Pheumalogy (From 2006-07)	Y		
263 = Paediatric Diabetic Medicine	Y		
264 = Paediatric Cystic Fibrosis	Y		
280 = Paediatric Interventional Radiology (From 2006-07)	Y		
290 = Community Paediatrics (From 2006-07)	Y		
291 = Paediatric Neuro-Disability (From 2006-07)	Y		
300 = General Medicine		Y	
301 = Gastroenterology		Y	
302 = Endocrinology		Y	
303 = Clinical Haematology		Y	
304 = Clinical Physiology (From 2008-09)		Y	
305 = Clinical Pharmacology		Y	
306 = Hepatology		Y	
307 = Diabetic Medicine		Y	
308 = Bone And Marrow Transplantation (Previously Part Of Clinical Haematology)		Y	
309 = Haemophilia (Previously Part Of Clinical Haematology)		Y	
310 = Audiological Medicine		Y	
311 = Clinical Genetics		Y	
313 = Clinical Immunology And Allergy		Y	
314 = Rehabilitation Service		Y	

315 = Palliative Medicine		Y	
316 = Clinical Immunology		Y	
317 = Allergy Service		Y	
318 = Intermediate Care		Y	
319 = Respite Care		Y	
320 = Cardiology		Y	
321 = Paediatric Cardiology	Y		
322 = Clinical Microbiology		Y	
323 = Spinal Injuries (From 2006-07)		Y	
324 = Anticoagulant Service		Y	
325 = Sport And Exercise Medicine		Y	
327 = Cardiac Rehabilitation		Y	
328 = Stroke Medicine		Y	
329 = Transient Ischaemic Attack		Y	
330 = Dermatology		Y	
331 = Congenital Heart Disease Service (From April 2013)		Y	
340 = Respiratory Medicine (Previously Known As Thoracic Medicine)		Y	
341 = Respiratory Physiology (Previously Known As Sleep Studies)		Y	
342 = Programmed Pulmonary Rehabilitation		Y	
343 = Adult Cystic Fibrosis Service		Y	
344 = Complex Specialised Rehabilitation Service (From April 2013)		Y	
345 = Specialist Rehabilitation Service (From April 2013)		Y	
346 = Local Specialist Rehabilitation Service (From April 2013)		Y	
350 = Infectious Diseases		Y	
352 = Tropical Medicine		Y	
360 = Genitourinary Medicine		Y	
361 = Nephrology		Y	
370 = Medical Oncology		Y	
371 = Nuclear Medicine (From 2008-09)		Y	
400 = Neurology		Y	
401 = Clinical Neurophysiology (From 2008-09)		Y	
410 = Rheumatology		Y	
420 = Paediatrics	Y		
421 = Paediatric Neurology	Y		
422 = Neonatology		Y	
424 = Well Babies (Care Given By The Mother/Substitute, With Nursing AdviceNeeded)		Y	
430 = Geriatric Medicine		Y	
450 = Dental Medicine Specialities		Y	
460 = Medical Ophthalmology		Y	
501 = Obstetrics		Y	
502 = Gynaecology		Y	
503 = Gynaecological Oncology		Y	
560 = Midwifery Service		Y	
650 = Physiotherapy (From 2006-07)			Y
651 = Occupational Therapy (From 2006-07)		Y	

652 = Speech And Language Therapy (From 2006-07)		Y	
653 = Podiatry (From 2006-07)		Y	
654 = Dietetics (From 2006-07)			Y
655 = Orthoptics (From 2006-07)		Y	
656 = Clinical Psychology (From 2006-07)			Y
657 = Prosthetics		Y	
658 = Orthotics		Y	
659 = Drama Therapy		Y	
660 = Art Therapy		Y	
661 = Music Therapy		Y	
662 = Optometry		Y	
663 = Podiatric Surgery (From April 2013)		Y	
700 = Learning Disability (Previously Known As Mental Handicap)		Y	
710 = Adult Mental Illness		Y	
711 = Child And Adolescent Psychiatry	Y		
712 = Forensic Psychiatry		Y	
713 = Psychotherapy		Y	
715 = Old Age Psychiatry		Y	
720 = Eating Disorders (From 2006-07)		Y	
721 = Addiction Services (From 2006-07)		Y	
722 = Liaison Psychiatry (From 2006-07)		Y	
723 = Psychiatric Intensive Care(From 2006-07)		Y	
724 = Perinatal Psychiatry (From 2006-07)		Y	
725 = Mental Health Recovery And Rehabilitation Service (From April 2013)		Y	
726 = Mental Health Dual Diagnosis Service (From April 2013)		Y	
727 = Dementia Assessment Service (From April 2013)		Y	
800 = Clinical Oncology (Previously Known As Radiotherapy)		Y	
811 = Interventional Radiology		Y	
812 = Diagnostic Imaging (From 2008-09)			Y
822 = Chemical Pathology		Y	
834 = Medical Virology		Y	
840 = Audiology (From 2008-09)		Y	
920 = Diabetic Education Service (From April 2013)			Y
Consultant Main Specialty	Paediatric	Adult	Unclassified
100 = General Surgery		Y	
101 = Urology		Y	
110 = Trauma And Orthopaedics		Y	
120 = Ear, Nose And Throat (Ent)		Y	
130 = Ophthalmology		Y	
140 = Oral Surgery		Y	
141 = Restorative Dentistry		Y	
142 = Paediatric Dentistry (Available From 1999-2000)		Y	
143 = Orthodontics		Y	
145 = Oral And Maxillo Facial Surgery (Available From 2004-05)		Y	
146 = Endodontics (Available From 2004-05)		Y	

147 = Periodontics		Y	
148 = Prosthodontics (Available From 2004-05)		Y	
149 = Surgical Dentistry (Available From 2004-05)		Y	
150 = Neurosurgery		Y	
160 = Plastic Surgery		Y	
170 = Cardiothoracic Surgery		Y	
171 = Paediatric Surgery	Y		
180 = Accident And Emergency (EMERGENCY DEPARTMENT)			Y
190 = Anaesthetics		Y	
191 = Pain Management (Available From 1998-99 To 2003-04)		Y	
192 = Critical Care Medicine (Available From 2004-05)		Y	
300 = General Medicine		Y	
301 = Gastroenterology		Y	
302 = Endocrinology		Y	
303 = Clinical Haematology		Y	
304 = Clinical Physiology		Y	
305 = Clinical Pharmacology		Y	
310 = Audiological Medicine		Y	
311 = Clinical Genetics		Y	
312 = Clinical Cytogenics And Molecular Genetics (Available From 1990-91)		Y	
313 = Clinical Immunology And Allergy (Available From 1991-92)		Y	
314 = Rehabilitation (Available From 1991-92)		Y	
315 = Palliative Medicine		Y	
320 = Cardiology		Y	
321 = Paediatric Cardiology (Available From 2004-05)	Y		
325 = Sport And Exercise Medicine		Y	
326 = Acute Internal Medicine		Y	
330 = Dermatology		Y	
340 = Respiratory Medicine (Also Known As Thoracic Medicine)		Y	
350 = Infectious Diseases		Y	
352 = Tropical Medicine (Available From 2004-05)		Y	
360 = Genito-Urinary Medicine		Y	
361 = Nephrology		Y	
370 = Medical Oncology		Y	
371 = Nuclear Medicine		Y	
400 = Neurology		Y	
401 = Clinical Neuro-Physiology		Y	
410 = Rheumatology		Y	
420 = Paediatrics	Y		
421 = Paediatric Neurology	Y		
430 = Geriatric Medicine		Y	
450 = Dental Medicine (Available From 1990-91)		Y	
451 = Special Care Dentistry		Y	
460 = Medical Ophthalmology (Available From 1993-94)		Y	

499 = Non-Uk Provider - Specialty Function Not Known, Treatment Mainly Medical		Y	
500 = Obstetrics And Gynaecology		Y	
501 = Obstetrics (Prior To 2004-05: Obstetrics For Patients Using A Hospital Bed Or Delivery Facilities)		Y	
502 = Gynaecology		Y	
504 = Community Sexual And Reproductive Health		Y	
560 = Midwifery (Available From October 1995)		Y	
600 = General Medical Practice		Y	
601 = General Dental Practice		Y	
610 = General Practice With Maternity Function (Available To 2003-04)		Y	
620 = General Practice Other Than Maternity (Available To 2003-04)		Y	
700 = Learning Disability (Previously Known As Mental Handicap)		Y	
710 = Adult Mental Illness		Y	
711 = Child And Adolescent Psychiatry			Y
712 = Forensic Psychiatry		Y	
713 = Psychotherapy		Y	
715 = Old Age Psychiatry (Available From 1990-91)		Y	
800 = Clinical Oncology (Previously Radiotherapy)		Y	
810 = Radiology		Y	
820 = General Pathology		Y	
821 = Blood Transfusion		Y	
822 = Chemical Pathology		Y	
823 = Haematology		Y	
824 = Histopathology		Y	
830 = Immunopathology		Y	
831 = Medical Microbiology And Virology		Y	
832 = Neuropathology (Available To 2003-04)		Y	
833 = Medical Microbiolody		Y	
834 = Medical Virology		Y	
900 = Community Medicine		Y	
901 = Occupational Medicine		Y	
902 = Community Health Services - Dental (Available From 2004-05)		Y	
903 = Public Health Medicine (Available From 2004-05)		Y	
904 = Public Health Dental (Available From 2004-05)		Y	
950 = Nursing Episode (Available From 2002-03)		Y	
960 = Allied Health Professional Episode (Available From 2006-07)		Y	

A2.2.3 Supplementary material S3: Sensitivity analyses

Sampling timeframe

Healthcare use is known to vary with age. Age has the potential to be a confounder to the variable of interest (transition status) as those in adult care will generally be older than those in paediatric care. Sufficient years of data are needed to separate associations of the outcomes with age and with transition status. Inclusion of too many years decreases sample size (as it restricts to the models to individuals present for longer) and may underestimate short term associations with transition (effects of transition may be mostly short term, lasting a few years). Longer sampling timeframes may also introduce bias: for example, young people may change primary health care provider and leave the dataset around age 18 years if they move for education or employment and may differ from those who remain.

At least three years of data are needed, with at least two either in adult or paediatric healthcare to ensure age and transition status are not entirely collinear (over only two years of data, associations with age and transition would be indistinguishable). An a priori decision was made to use the last two years of paediatric data and first two years of adult data per cohort member and it was required that all cohort members were present in the data for at least these years. For the regressions, sensitivity analyses were conducted with all possible combinations of two, three and four years of paediatric data and one, two, three or four years of adult data.

Effects of sampling timeframe

Regressions were run with 2-4 years of data while in paediatric care and 1-4 years of data while in adult care.

Effects on incidence rate ratios dependent on transition status and age in year

Incidence rate ratios for the outcomes of emergency inpatient admissions and Emergency Department visits dependent on being in adult (compared to paediatric) healthcare and per year of age for males and females are shown in Figure S2, for the range of sampling timeframes tested.

The major differences are between regressions using one year of data when the young person was in adult healthcare or more than one year of data. Other variations in pre- and post-transition sampling years produce incidence rate ratios that have overlapping confidence intervals for the outcomes dependent on being in adult compared to paediatric care across all categories of condition and for the outcomes dependent on year of age except for the Emergency Department visits in the no long-term conditions group.

A key point is that when only one year of adult data is used, compared to those when more years of adult data are used, incidence rate ratios for the outcomes differ in opposing directions for being in adult (compared to paediatric) healthcare and age. This suggests a different model fit when only one year of adult data is used, with change sin outcomes being associated with changes in age rather than changes in healthcare. It is to be expected that too short a time period of data would make it more difficult to distinguish between associations with age and associations with transition status. This, and the apparent stability of incidence rate ratios once two or more years of adult data are used, suggests that it is the regressions using two or more years of data that most closely match the real associations between the outcomes, age and transition status.

Observations on model fit to all available data

Observed mean emergency inpatient admissions (Figure S3) and Emergency Department visits per person year (Figure S4) are plotted for the whole cohort using all data available from age 12 to 23 years, along with expected values from the regression models for the same population and age

range. It should be noted that the models were developed on a subset of these data: 2-4 years of data while in paediatric care and 1-4 years of data while in adult care, as indicated in the figures. Models and observations therefore sometimes diverge for ages for which there were few individuals included in the sample used to generate the models - for example, transition for young people with no long-term conditions was set to 16 years, so no young people were included when over 19 years of age (the largest sampling timeframe was four years of adult data, ending for this group at age 19 years).

Figures S3 and S4 demonstrate poor fit when only one year of adult data is used, particularly for emergency inpatient admissions (Figure 2). Differences for other sampling timeframes are much less marked, although there is observable worse fit for some of the lines using two years of paediatric data compared to three or four years of paediatric data (in particular, for emergency inpatient admissions for females with diabetes (Figure 2) and for Accident and Emergency visits for males with diabetes or no long-term conditions (Figure 3).

Appropriate choices of sampling time frame

Given the above, and the objectives set out in the main text regarding sampling timeframe selection, at least two years of paediatric and adult data appear to be required and the exact choice of sampling timeframe beyond that does not greatly change the conclusions drawn .

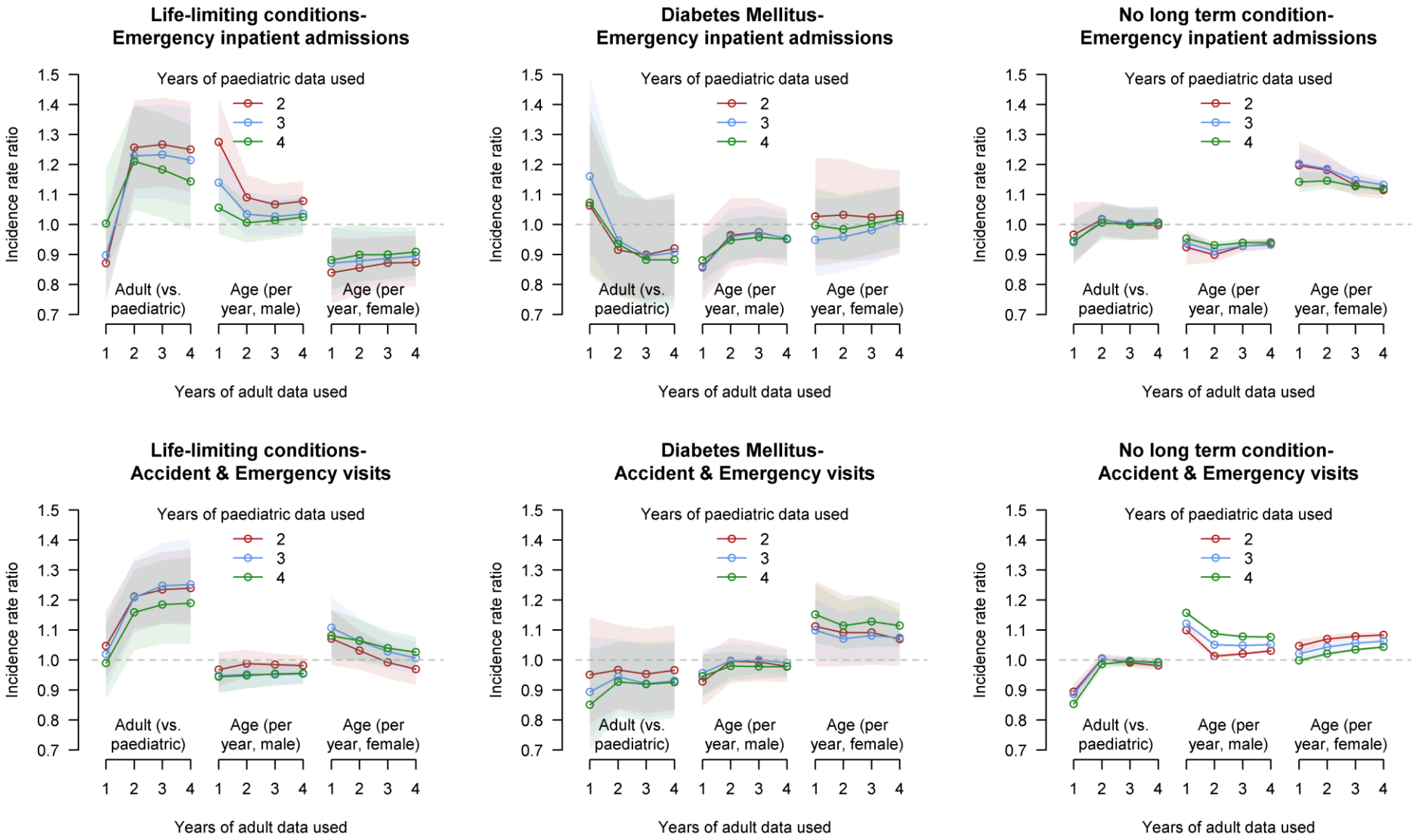

Figure S2: Incidence rate ratios for emergency inpatient admissions and Emergency Department visits associated with being in adult healthcare (versus paediatric healthcare) and per year of age for males and females, depending on the years of data pre- and post-transition used in the regressions. Shaded regions indicate 95% confidence intervals.

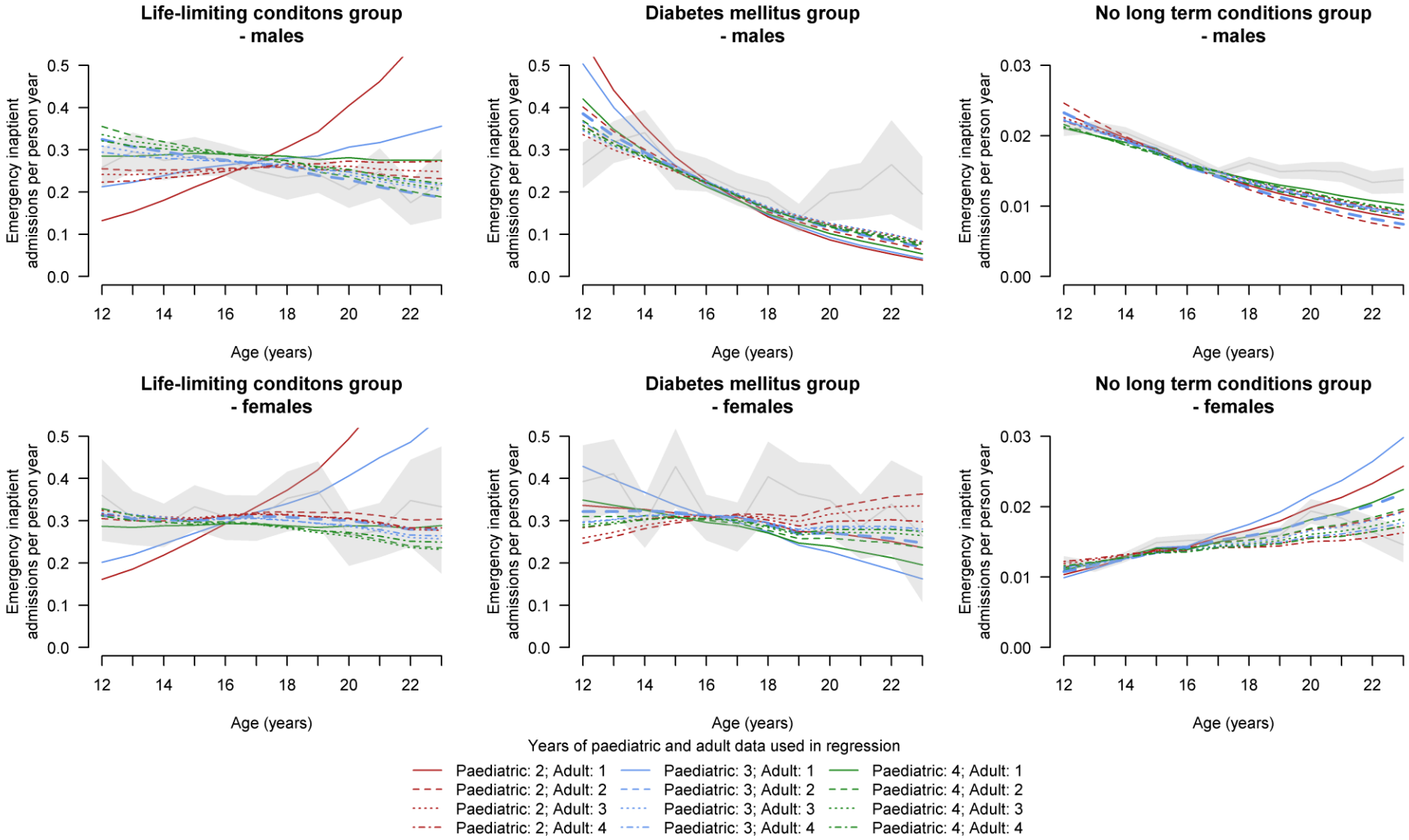

Figure S3: Fits of predicted numbers of emergency inpatient admissions per person per year by age from the models (with indicated years of data used) against all available data for cohort members.

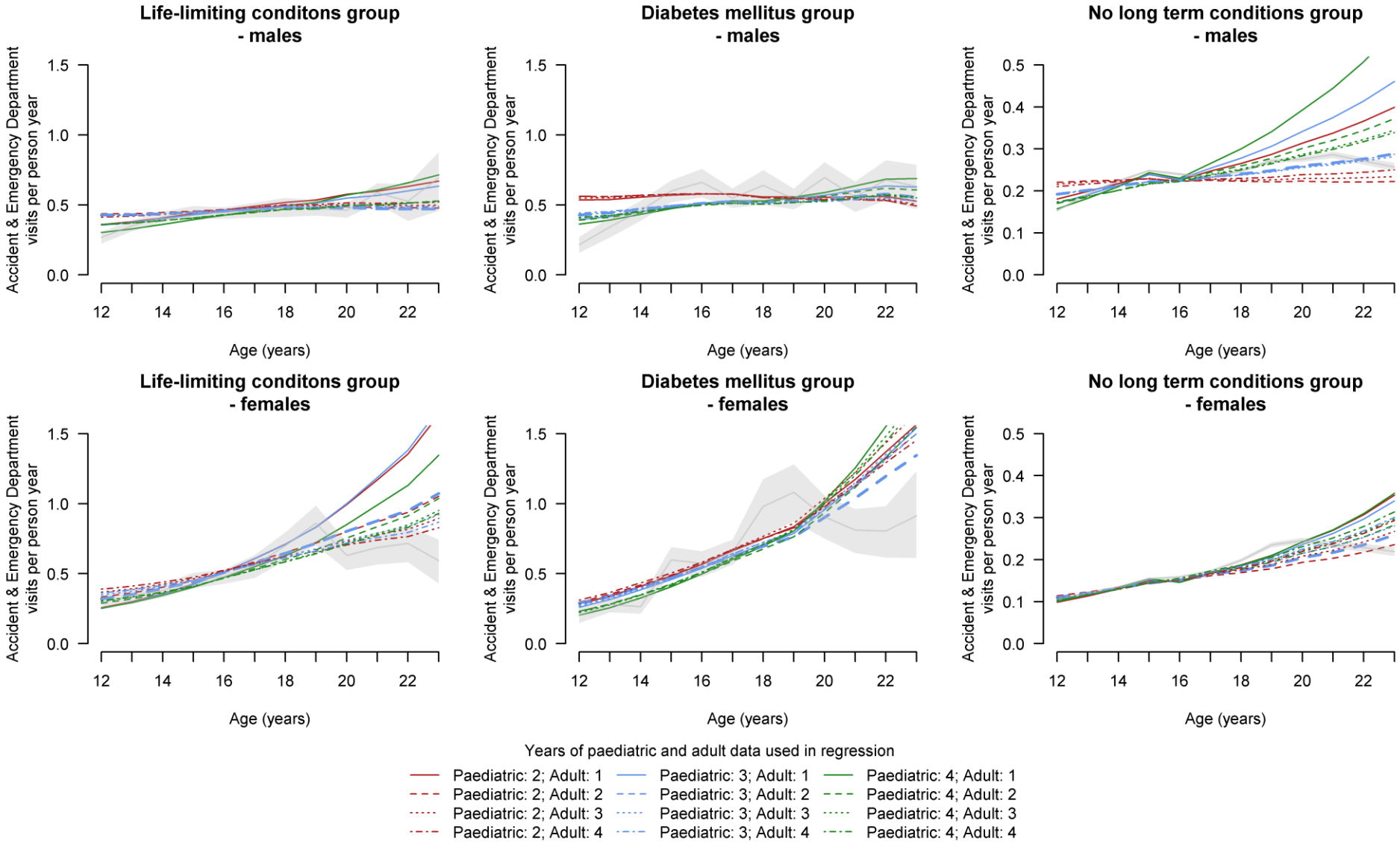

Figure S4: Fits of predicted numbers of Emergency Department visits per person per year by age from the models (with indicated years of data used) against all available data for cohort members.

Minimum age at exit from dataset required to have transition assigned

The results were insensitive to variations in the required minimum age at exit from the dataset required for transition to be set to 16 years in the absence of sufficient data to estimate transition (Table S3 and S4). In practice, few individuals were present for long enough to have data for the last two years of paediatric care and first two years of adult care with a transition age of 16 years (i.e. present from at least age 14-17 years) for these decisions to have much impact.

Table S3: Regression model incidence rate ratio for two level Poisson regressions on the numbers of emergency inpatient admissions and number of Emergency Department visits per cohort member per year when restrictions on age at exit from the dataset to have transition assigned are removed. *indicates there are omitted combinations of interactions (reference groups with incident rate ratio 1).

	Emergency inpatient admissions				Emergency Department visits			
	Incidence rate ratio	95% confidence interval		P value	Incidence rate ratio	95% confidence interval		P value
Age (per year of age)	0.90	0.87	0.93	<0.01	1.02	1.01	1.03	<0.01
Sex								
Male	1 (ref)				1 (ref)			
Female	0.06	0.03	0.12	<0.01	0.22	0.18	0.28	<0.01
Condition group								
No long-term condition	1 (ref)				1 (ref)			
Diabetes	16.03	2.12	121.21	0.01	3.12	0.80	12.13	0.10
Life-limiting condition	5.04	1.44	17.60	0.01	2.97	1.36	6.49	0.01
Transition status								
Paediatric care	1 (ref)				1 (ref)			
Adult care	1.00	0.95	1.06	0.95	1.01	0.99	1.02	0.43
Sex × Age interaction*								
Female (per year of age)	1.19	1.13	1.24	<0.01	0.22	0.18	0.28	<0.01
Condition group × Age interaction*								
Diabetes (per year of age)	0.99	0.88	1.12	0.93	0.98	0.91	1.06	0.70
Life-limiting conditions (per year of age)	1.08	1.00	1.16	0.05	0.98	0.93	1.03	0.35
Condition group × Sex × Age interaction*								
Diabetes and female (per year of age)	1.01	0.85	1.20	0.92	1.12	0.99	1.26	0.07
Life-limiting conditions and female (per year of age)	0.85	0.75	0.96	0.01	1.04	0.97	1.11	0.31
Condition group × Transition status interaction*								
Diabetes and adult care	0.82	0.67	1.01	0.07	0.93	0.82	1.06	0.30
Life-limiting condition and adult care	1.32	1.15	1.51	<0.01	1.23	1.11	1.37	<0.01

Table S4: Combined incidence rate ratios (taking account of interactions) for emergency inpatient admissions and Emergency Department visits when restrictions on age at exit from the dataset to have transition assigned are removed.

Group	Emergency inpatient admissions				Emergency Department visits			
	Incidence rate ratio (adult compared to paediatric care)	95% confidence interval		P value	Incidence rate ratio (adult compared to paediatric care)	95% confidence interval		P value
Life-limiting conditions	1.32	1.17	1.50	<0.01	1.24	1.12	1.37	<0.01
Diabetes	0.83	0.68	1.01	0.06	0.94	0.83	1.07	0.34
No long-term conditions	1.00	0.95	1.06	0.95	1.01	0.99	1.02	0.43

Exclusion of ethnic group and deprivation group

Inclusion or exclusion of ethnic group and deprivation group had little effect on incidence rate ratios for other variables in the models (Table S5 and S6). Ethnic group and deprivation group were both at level 1 (individual) and so were partly accounted for by the use of a random intercept in the models.

Table S5: Regression model incidence rate ratio for two level Poisson regressions on the numbers of emergency inpatient admissions and number of Emergency Department visits per cohort member per year when ethnic group and deprivation category are excluded from the models. *indicates there are omitted combinations of interactions (reference groups with incident rate ratio 1).

	Emergency inpatient admissions				Emergency Department visits			
	Incidence rate ratio	95% confidence interval		P value	Incidence rate ratio	95% confidence interval		P value
Age (per year of age)	0.90	0.87	0.93	<0.01	1.02	1.01	1.03	<0.01
Sex								
Male	1 (ref)				1 (ref)			
Female	0.06	0.03	0.12	<0.01	0.22	0.18	0.28	<0.01
Condition group								
No long-term condition	1 (ref)				1 (ref)			
Diabetes	16.16	2.14	121.97	0.01	3.16	0.81	12.29	0.10
Life-limiting condition	6.32	1.80	22.16	<0.01	3.39	1.54	7.47	<0.01
Transition status								
Paediatric care	1 (ref)				1 (ref)			
Adult care	1.00	0.95	1.06	0.95	1.01	0.99	1.02	0.43
Sex × Age interaction*								
Female (per year of age)	1.19	1.13	1.24	<0.01	1.07	1.06	1.09	<0.01
Condition group × Age interaction*								
Diabetes (per year of age)	0.99	0.88	1.12	0.92	0.98	0.91	1.06	0.69
Life-limiting conditions (per year of age)	1.07	0.99	1.15	0.10	0.97	0.92	1.02	0.26
Condition group × Sex × Age interaction*								
Diabetes and female (per year of age)	1.01	0.85	1.20	0.92	1.12	0.99	1.26	0.07
Life-limiting conditions and female (per year of age)	0.85	0.76	0.96	0.01	1.04	0.96	1.11	0.33
Condition group × Transition status interaction*								
Diabetes and adult care	0.82	0.67	1.01	0.07	0.93	0.82	1.06	0.30
Life-limiting condition and adult care	1.33	1.16	1.53	<0.01	1.24	1.12	1.37	<0.01

Table S6: Combined incidence rate ratios (taking account of interactions) for emergency inpatient admissions and Emergency Department visits when ethnic group and deprivation category are excluded from the models

Group	Emergency inpatient admissions				Emergency Department visits			
	Incidence rate ratio (adult compared to paediatric care)	95% confidence interval		P value	Incidence rate ratio (adult compared to paediatric care)	95% confidence interval		P value
Life-limiting conditions	1.33	1.18	1.51	<0.01	1.25	1.13	1.38	<0.01
Diabetes	0.83	0.68	1.01	0.06	0.94	0.83	1.07	0.35
No long-term conditions	1.00	0.95	1.06	0.95	1.01	0.99	1.02	0.43

Inclusion of year of birth

Inclusion or year of birth for possible cohort effects (e.g. a young person born in 1992 experiencing different care and transition or being at a different stage of condition at transition age to a young person born in 2001) had little effect on incidence rate ratios for other variables in the models and on the combined associations of the outcomes with transition for each condition group (Tables S7 and S8).

Table S7: Regression model incidence rate ratio for two level Poisson regressions on the numbers of emergency inpatient admissions and number of Emergency Department visits per cohort member per year when year f birth is included in the models. *indicates there are omitted combinations of interactions (reference groups with incident rate ratio 1).

	Emergency inpatient admissions				Emergency Department visits			
	Incidence rate ratio	95% confidence interval		P value	Incidence rate ratio	95% confidence interval		P value
Age (per year of age)	0.90	0.87	0.93	<0.01	1.02	1.01	1.03	<0.01
Year of birth (per year)	0.99	0.98	1.00	0.03	1.07	1.06	1.07	<0.01
Sex								
Male	1 (ref)				1 (ref)			
Female	0.90	0.87	0.93	<0.01	0.22	0.17	0.27	<0.01
Condition group								
No long-term condition	1 (ref)				1 (ref)			
Diabetes	15.95	2.12	119.93	0.01	3.42	0.87	13.45	0.08
Life-limiting condition	6.37	1.82	22.25	<0.01	2.82	1.30	6.13	0.01
Transition status								
Paediatric care	1 (ref)				1 (ref)			
Adult care	1.00	0.95	1.06	0.94	1.00	0.99	1.02	0.56
Sex × Age interaction*								
Female (per year of age)	1.19	1.13	1.24	<0.01	1.07	1.06	1.09	<0.01
Condition group × Age interaction*								
Diabetes (per year of age)	0.99	0.88	1.12	0.93	0.98	0.91	1.06	0.68
Life-limiting conditions (per year of age)	1.07	0.99	1.15	0.10	0.98	0.94	1.03	0.50
Condition group × Sex × Age interaction*								
Diabetes and female (per year of age)	1.01	0.85	1.20	0.92	1.12	0.99	1.26	0.06
Life-limiting conditions and female (per year of age)	0.85	0.76	0.96	0.01	1.04	0.96	1.11	0.34
Condition group × Transition status interaction*								
Diabetes and adult care	0.82	0.67	1.01	0.07	0.93	0.82	1.06	0.30
Life-limiting condition and adult care	1.33	1.16	1.53	<0.01	1.23	1.11	1.36	<0.01

Table S8: Combined incidence rate ratios (taking account of interactions) for emergency inpatient admissions and Emergency Department visits when year of birth is included in the models.

Group	Emergency inpatient admissions	Emergency Department visits

	Incidence rate ratio (adult compared to paediatric care)	95% confidence interval		P value	Incidence rate ratio (adult compared to paediatric care)	95% confidence interval		P value
Life-limiting conditions	1.33	1.18	1.51	<0.01	1.23	1.12	1.36	<0.01
Diabetes	0.83	0.68	1.01	0.06	0.94	0.83	1.07	0.33
No long-term conditions	1.00	0.95	1.06	0.94	1.00	0.99	1.02	0.56

A2.2.4 Supplementary material S4: Age group splits for population estimates

Table S9: Estimated population levels of excess emergency inpatient admissions and excess Emergency Department visits each year for young people aged 14 to 23 years with life-limiting conditions in England in their first two years of adult care.

Age group	Number with life-limiting conditions in England	% in first two years of adult healthcare	Number in first two years of adult healthcare	Emergency inpatient admissions			Emergency Department visits		
				Expected in paediatric healthcare	Expected in adult healthcare	Excess associated with transition	In paediatric healthcare	In adult healthcare	Excess associated with transition
14-17	12495	22.90657	2862	809	1044	235	1381	1719	338
18-23	19324	34.52585	6672	1785	2302	518	3524	4387	863
14-23	**31819**	**27.94478**	**9534**	**2594**	**3346**	**753**	**4905**	**6106**	**1201**

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A2.3 Supplementary materials for paper 5: GPs' role in caring for children and young people with life-limiting conditions: a retrospective cohort study

A2.3.1 Additional figures and tables

Figure 1: Construction of the cohort and datasets used.

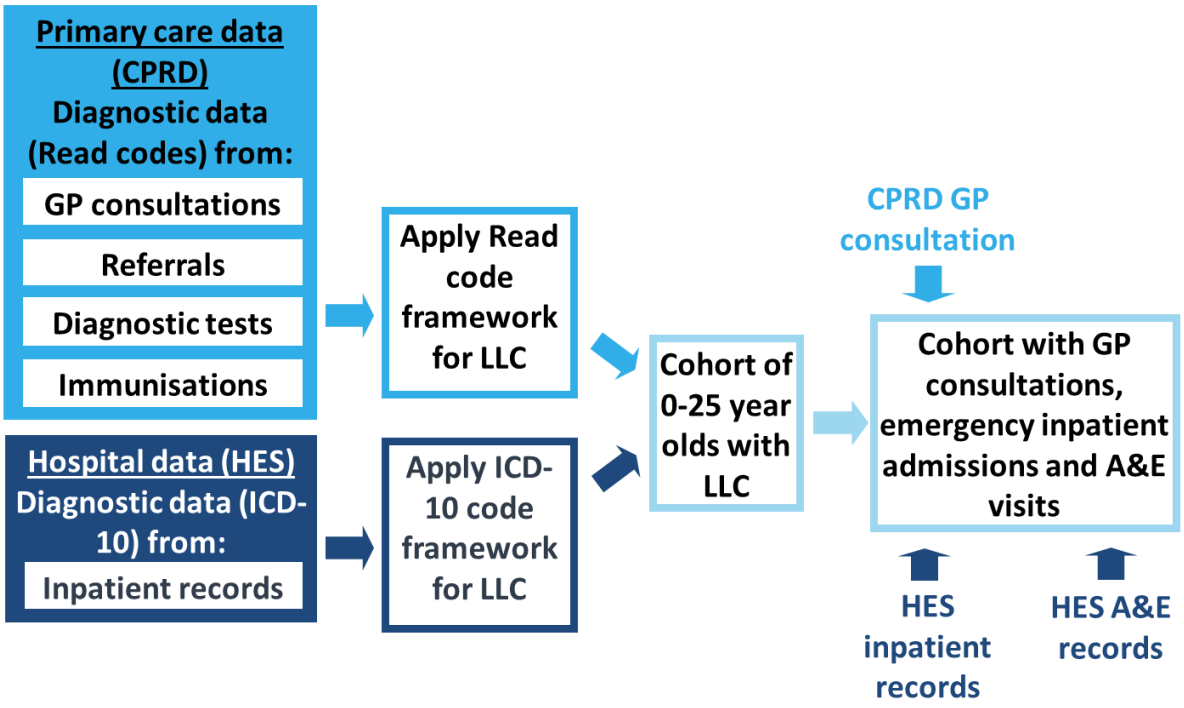


Figure 2: Face to face GP consultations per person year by age in the cohort, 2000-2015.

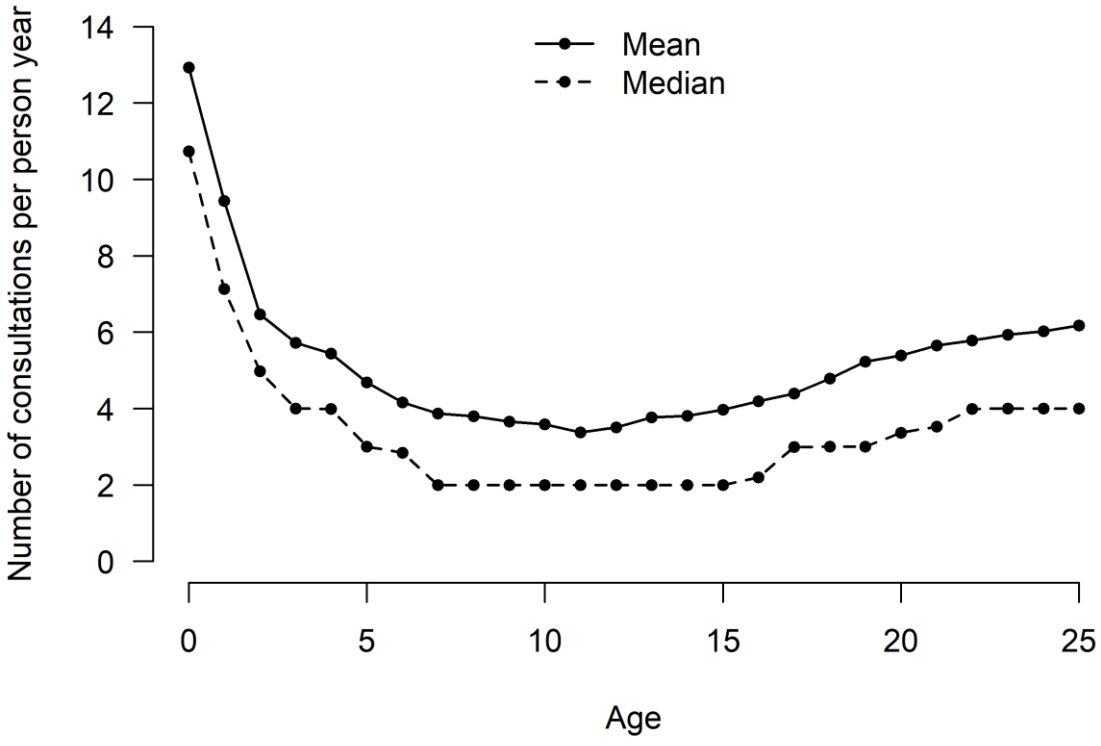


Table 1: Study cohort and demographics, emergency inpatient and A&E activity. Cell values of 10 or less are censored ('≤10') and some other cells with values over 10 are censored to prevent censored cells being determined by differencing ('*').

	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	Total
Individuals	2293	3184	3988	4668	5364	5969	6594	7257	7766	8237	8753	8985	9033	9055	8383	6963	19888
Gender																	
Female	996	1422	1794	2104	2378	2649	2912	3201	3470	3678	3937	4058	4035	4057	3731	3080	9222
Male	1297	1762	2194	2564	2986	3320	3682	4056	4296	4559	4816	4927	4998	4998	4652	3883	10666
Ethnic group																	
Black African	13	27	38	47	56	71	88	108	118	128	150	172	187	213	206	180	430
Black Caribbean	13	17	27	25	35	42	49	54	51	49	54	59	62	68	60	47	143
Black Other	≤10	13	22	22	30	38	40	41	42	52	55	57	61	64	54	46	147
Bangladeshi	≤10	≤10	≤10	14	23	23	30	35	39	37	37	45	50	57	44	40	94
Chinese	≤10	≤10	*	15	19	20	21	16	16	21	26	28	31	32	26	24	63
Indian	24	39	45	55	69	83	98	107	117	141	146	162	170	177	172	114	338
Pakistani	21	39	59	84	102	116	132	163	175	179	212	237	249	241	205	184	463
Other Asian	≤10	13	16	24	37	42	58	73	87	89	109	126	144	145	146	107	277
White	2030	2808	3473	4047	4585	5113	5607	6130	6556	6942	7329	7445	7395	7351	6800	5636	16228
Mixed	21	32	41	54	85	89	109	140	153	163	184	214	242	242	234	212	483
Other	27	32	40	55	59	65	81	92	105	130	157	162	168	177	173	141	377
Unknown	117	147	204	226	264	267	281	298	307	306	294	278	274	288	263	232	845
Age group																	
Under 1	107	128	123	126	148	181	182	209	198	233	223	218	224	241	158	110	N/A
1 to 5	618	868	1084	1239	1399	1509	1599	1701	1757	1792	1907	1962	1981	1936	1750	1376	N/A
6 to 10	511	674	835	977	1117	1290	1460	1587	1684	1781	1867	1868	1837	1868	1776	1507	N/A
11 to 15	426	554	718	835	957	1033	1179	1339	1433	1539	1654	1718	1738	1696	1651	1401	N/A
16 to 20	365	512	601	739	826	1002	1102	1242	1382	1462	1521	1613	1621	1639	1539	1315	N/A
21 to 25	266	448	627	752	917	954	1072	1179	1312	1430	1581	1606	1632	1675	1509	1254	N/A
Main diagnostic group																	
Circulatory	50	78	97	132	154	170	183	197	201	216	232	238	237	234	198	152	588
Congenital	845	1189	1521	1803	2109	2353	2570	2837	3022	3241	3434	3530	3559	3585	3328	2774	6741
Gastrointestinal	19	34	35	37	46	66	81	98	101	104	136	144	137	135	129	99	338
Genitourinary	106	167	202	233	255	285	316	356	376	396	425	442	450	452	423	361	1151

Haematology	75	107	134	173	209	251	298	335	363	400	443	476	496	519	481	398	1118
Metabolic	89	107	135	172	192	222	258	271	298	316	352	372	359	339	305	285	783
Neurology	381	514	653	757	859	931	1011	1116	1198	1227	1279	1285	1262	1233	1124	911	2863
Oncology	430	603	773	867	988	1074	1219	1307	1410	1476	1528	1511	1476	1452	1316	1103	4051
Perinatal	14	27	31	38	47	65	74	92	104	121	136	151	169	196	214	184	347
Respiratory	264	332	372	409	454	487	511	564	606	660	707	747	796	812	767	616	1667
Other	20	26	35	47	51	65	73	84	87	80	81	89	92	98	98	80	241
Deprivation category																	
1 (least deprived)	475	667	801	940	1065	1158	1311	1444	1573	1698	1825	1837	1826	1791	1722	475	3774
2	485	650	822	948	1104	1229	1370	1525	1577	1693	1803	1810	1768	1738	1629	485	3845
3	480	650	806	932	1066	1165	1281	1385	1474	1552	1634	1670	1690	1697	1551	480	3825
4	428	605	774	922	1061	1196	1319	1444	1570	1640	1745	1840	1864	1914	1740	428	4203
5 (most deprived)	420	606	779	919	1061	1217	1307	1453	1565	1647	1740	1822	1879	1908	1737	420	4222
Unknown	≤10	≤10	≤10	≤10	≤10	≤10	≤10	≤10	≤10	≤10	≤10	≤10	≤10	≤10	≤10	≤10	19
Face to face GP consultations (mean per person)	12868 (7.12)	15427 (6.04)	18794 (5.61)	22830 (5.67)	24537 (5.30)	26934 (5.18)	29017 (5.01)	30394 (4.79)	32444 (4.73)	35574 (4.87)	36473 (4.74)	37309 (4.75)	38498 (4.82)	36936 (4.75)	31591 (4.55)	25020 (4.43)	45464 6
Usual provider of care index																	
< 1/2	578	716	899	1154	1319	1568	1690	1825	2040	2371	2494	2545	2648	2486	2189	1716	N/A
≥1/2, <2/3	501	718	853	1069	1117	1287	1381	1552	1556	1735	1749	1860	1852	1795	1661	1291	N/A
≥ 2/3	542	720	870	893	992	1040	1124	1258	1324	1312	1314	1267	1313	1291	1113	891	N/A
Undefined^	672	1030	1366	1552	1936	2074	2399	2622	2846	2819	3196	3313	3220	3483	3420	3065	N/A
Coefficient of variation of gaps between consultations																	
< 0.75	483	757	837	1019	1082	1215	1341	1405	1547	1524	1682	1663	1693	1674	1497	1124	N/A
≥0.75, < 0.95	336	483	603	691	752	905	946	1000	1064	1194	1251	1298	1316	1256	1047	834	N/A
≥0.95, < 1.20	294	419	552	647	730	895	913	1006	1063	1232	1287	1286	1272	1263	1153	914	N/A
≥1.20	224	321	455	566	686	689	804	1014	1013	1272	1114	1229	1300	1177	1091	912	N/A
Undefined ^	956	1204	1541	1745	2114	2265	2590	2832	3079	3015	3419	3509	3452	3685	3595	3179	N/A
Emergency inpatient admissions (mean per person)	1691 (0.94)	2394 (0.94)	2661 (0.79)	2900 (0.72)	3074 (0.66)	3774 (0.73)	4089 (0.71)	4286 (0.68)	4628 (0.67)	4499 (0.62)	4732 (0.61)	4855 (0.62)	4796 (0.60)	4441 (0.57)	3893 (0.56)	3117 (0.55)	59830

A&E attendances (mean per person)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	4104 (0.60)	5064 (0.69)	5144 (0.67)	5701 (0.73)	5867 (0.73)	5845 (0.75)	5522 (0.80)	4318 (0.76)	41565

^Undefined due to having fewer than two consultations/gaps between consultations in the year

Table 2: Univariable analyses of variation in face to face GP consultations, emergency inpatient admissions and A&E attendances with cohort demographics.

	Face to face GP consultations per person year (95% CI)	Emergency inpatient admissions per person year (95% CI)	A&E attendances per person year (95% CI)	Mean usual provider of care index (SD)	Mean coefficient of variation for gaps between GP consultations (SD)
Gender					
Female	5.48 (5.45-5.50)	0.67 (0.66-0.68)	0.72 (0.71-0.73)	0.51 (0.22)	0.92 (0.37)
Male	4.54 (4.52-4.56)	0.64 (0.63-0.64)	0.71 (0.70-0.72)	0.52 (0.22)	0.92 (0.39)
Ethnic group					
Black African	4.42 (4.32-4.53)	0.62 (0.58-0.66)	0.81 (0.76-0.86)	0.50 (0.21)	0.90 (0.37)
Black Caribbean	4.58 (4.41-4.75)	0.85 (0.78-0.92)	1.08 (0.98-1.19)	0.50 (0.22)	0.87 (0.39)
Black Other	4.65 (4.46-4.83)	0.80 (0.72-0.88)	0.97 (0.87-1.08)	0.53 (0.22)	0.88 (0.39)
Bangladeshi	5.26 (5.04-5.47)	0.89 (0.80-0.98)	0.70 (0.61-0.80)	0.51 (0.21)	0.91 (0.36)
Chinese	5.02 (4.76-5.28)	0.48 (0.40-0.56)	0.61 (0.49-0.72)	0.50 (0.21)	0.92 (0.40)
Indian	4.70 (4.59-4.81)	0.67 (0.63-0.71)	0.64 (0.59-0.69)	0.51 (0.22)	0.91 (0.38)
Pakistani	6.13 (6.02-6.24)	0.91 (0.87-0.95)	0.85 (0.80-0.90)	0.52 (0.21)	0.92 (0.36)
Other Asian	5.78 (5.63-5.93)	0.91 (0.85-0.97)	1.08 (1.01-1.15)	0.51 (0.21)	0.91 (0.37)
White	5.03 (5.01-5.04)	0.66 (0.65-0.66)	0.71 (0.71-0.72)	0.51 (0.22)	0.92 (0.38)
Mixed	5.32 (5.22-5.43)	0.81 (0.77-0.85)	0.83 (0.78-0.88)	0.49 (0.21)	0.91 (0.38)
Other	4.65 (4.54-4.77)	0.78 (0.73-0.83)	0.96 (0.90-1.02)	0.53 (0.22)	0.92 (0.37)
Unknown	2.64 (2.58-2.69)	0.11 (0.10-0.12)	0.18 (0.16-0.19)	0.55 (0.22)	0.91 (0.41)
Age group					
Under 1	12.93 (12.72-13.15)	3.30 (3.19-3.41)	2.14 (2.02-2.26)	0.49 (0.21)	0.82 (0.33)
1 to 5	6.21 (6.18-6.24)	1.08 (1.06-1.09)	0.94 (0.93-0.96)	0.48 (0.21)	0.91 (0.35)
6 to 10	3.82 (3.80-3.85)	0.48 (0.47-0.49)	0.50 (0.49-0.51)	0.53 (0.22)	0.91 (0.38)
11 to 15	3.68 (3.65-3.71)	0.49 (0.48-0.50)	0.57 (0.56-0.58)	0.53 (0.22)	0.93 (0.40)
16 to 20	4.78 (4.74-4.81)	0.48 (0.47-0.49)	0.68 (0.67-0.70)	0.53 (0.22)	0.93 (0.40)
21 to 25	5.92 (5.88-5.96)	0.49 (0.48-0.50)	0.84 (0.82-0.85)	0.52 (0.22)	0.93 (0.39)

Main diagnostic group					
Circulatory	5.30 (5.20-5.39)	0.53 (0.50-0.56)	0.73 (0.69-0.78)	0.52 (0.22)	0.91 (0.38)
Congenital	4.57 (4.55-4.59)	0.41 (0.40-0.42)	0.59 (0.58-0.60)	0.50 (0.22)	0.92 (0.38)
Gastrointestinal	5.13 (5.00-5.26)	0.67 (0.63-0.72)	0.79 (0.73-0.85)	0.50 (0.21)	0.94 (0.40)
Genitourinary	6.01 (5.94-6.08)	0.92 (0.89-0.95)	1.23 (1.19-1.27)	0.52 (0.22)	0.94 (0.39)
Haematology	4.81 (4.74-4.87)	0.72 (0.69-0.74)	0.70 (0.67-0.73)	0.52 (0.22)	0.92 (0.39)
Metabolic	5.71 (5.63-5.79)	0.90 (0.87-0.93)	0.80 (0.76-0.84)	0.52 (0.23)	0.91 (0.38)
Neurology	5.56 (5.52-5.59)	0.72 (0.71-0.74)	0.83 (0.81-0.85)	0.52 (0.22)	0.91 (0.37)
Oncology	4.30 (4.27-4.34)	0.93 (0.92-0.95)	0.67 (0.66-0.69)	0.54 (0.22)	0.94 (0.40)
Perinatal	4.48 (4.37-4.59)	0.52 (0.48-0.56)	0.70 (0.65-0.75)	0.49 (0.21)	0.90 (0.38)
Respiratory	6.08 (6.03-6.14)	0.89 (0.87-0.91)	0.84 (0.82-0.87)	0.51 (0.22)	0.91 (0.36)
Other	5.20 (5.05-5.35)	0.50 (0.45-0.54)	0.76 (0.69-0.83)	0.52 (0.23)	0.91 (0.40)
Deprivation category					
1 (least deprived)	4.93 (4.90-4.96)	0.60 (0.59-0.61)	0.56 (0.54-0.57)	0.50 (0.21)	0.93 (0.39)
2	4.91 (4.88-4.94)	0.60 (0.58-0.61)	0.58 (0.57-0.60)	0.52 (0.22)	0.92 (0.38)
3	4.94 (4.91-4.97)	0.67 (0.66-0.68)	0.73 (0.71-0.74)	0.51 (0.22)	0.92 (0.38)
4	5.00 (4.97-5.03)	0.69 (0.68-0.71)	0.80 (0.78-0.81)	0.52 (0.22)	0.92 (0.38)
5 (most deprived)	5.00 (4.96-5.03)	0.70 (0.69-0.71)	0.92 (0.90-0.94)	0.52 (0.22)	0.91 (0.38)

A2.3.2 Data for figures in the main text

Data for figure 1

Gender	cohort age 0-4	cohort age 0-4 95%CI		population 0-4	cohort age 5-14	cohort age 5-14 95%CI		population age 5-14	cohort age 15-24	cohort age 15-24 95% CI		population age 15-24
Both	7.00	6.90	7.11	3.39	3.84	6.97	7.25	1.45	5.10	6.74	7.02	2.13
Male	7.11	3.79	3.89	3.51	3.76	3.69	3.82	1.39	4.12	3.88	4.03	1.34
Female	6.87	5.03	5.17	3.27	3.96	4.04	4.21	1.51	6.24	6.13	6.35	2.93

Data for figure 2

	usual provider of care index		coefficient of variation	
age	**mean**	**median**	**mean**	**median**
0	0.49	0.50	0.82	0.81
1	0.45	0.40	0.91	0.90
2	0.48	0.48	0.90	0.89
3	0.48	0.50	0.92	0.90
4	0.49	0.50	0.90	0.89
5	0.50	0.50	0.91	0.90
6	0.51	0.50	0.91	0.90
7	0.52	0.50	0.90	0.88
8	0.53	0.50	0.92	0.91
9	0.53	0.50	0.92	0.90
10	0.54	0.50	0.93	0.92
11	0.54	0.50	0.93	0.91
12	0.54	0.50	0.93	0.91
13	0.53	0.50	0.93	0.92
14	0.54	0.50	0.94	0.92
15	0.53	0.50	0.94	0.93
16	0.53	0.50	0.93	0.92
17	0.53	0.50	0.92	0.90
18	0.53	0.50	0.94	0.93
19	0.53	0.50	0.93	0.91
20	0.54	0.50	0.93	0.91
21	0.52	0.50	0.94	0.93
22	0.52	0.50	0.93	0.90
23	0.53	0.50	0.93	0.91
24	0.53	0.50	0.93	0.91
25	0.52	0.50	0.92	0.89

Data for figure 3

Age group	Emergency inpatient admissions per person year				A&E visits per person year			
	cohort	cohort 95% CI		population	cohort	cohort 95% CI		population
Under 1	4.02	3.12	5.21	0.33	2.23	1.92	2.56	0.74
1-4	1.27	1.10	1.43	0.10	1.20	1.14	1.27	0.51
5-9	0.42	0.35	0.49	0.04	0.61	0.57	0.65	0.29
10-14	0.36	0.29	0.44	0.04	0.57	0.53	0.60	0.34
15-19	0.36	0.30	0.43	0.05	0.67	0.57	0.80	0.38
20-24	0.45	0.37	0.54	0.06	0.84	0.75	0.93	0.45

Appendix 3: Data analysis plan for CPRD data (papers 3 and 4)

A3.1 Cohort generation

A3.1.1 General description

The aim is to end with a table (either existing in the database or created on demand from joins) with one row per individual per year when present in the dataset, with demographics, transition status, time present and time at risk in year and diagnostic groups and outcomes.

These are described below through text and diagrams of interactions between database tables, colour coded as follows:

blue: tables of data as provided by CPRD

red: tables of data from other sources - e.g. pre-existing coding frameworks, population data

grey: conceptual tables, indicating sub-stages in creation of other tables of data - never written to disk, if they exist at all it is only in memory

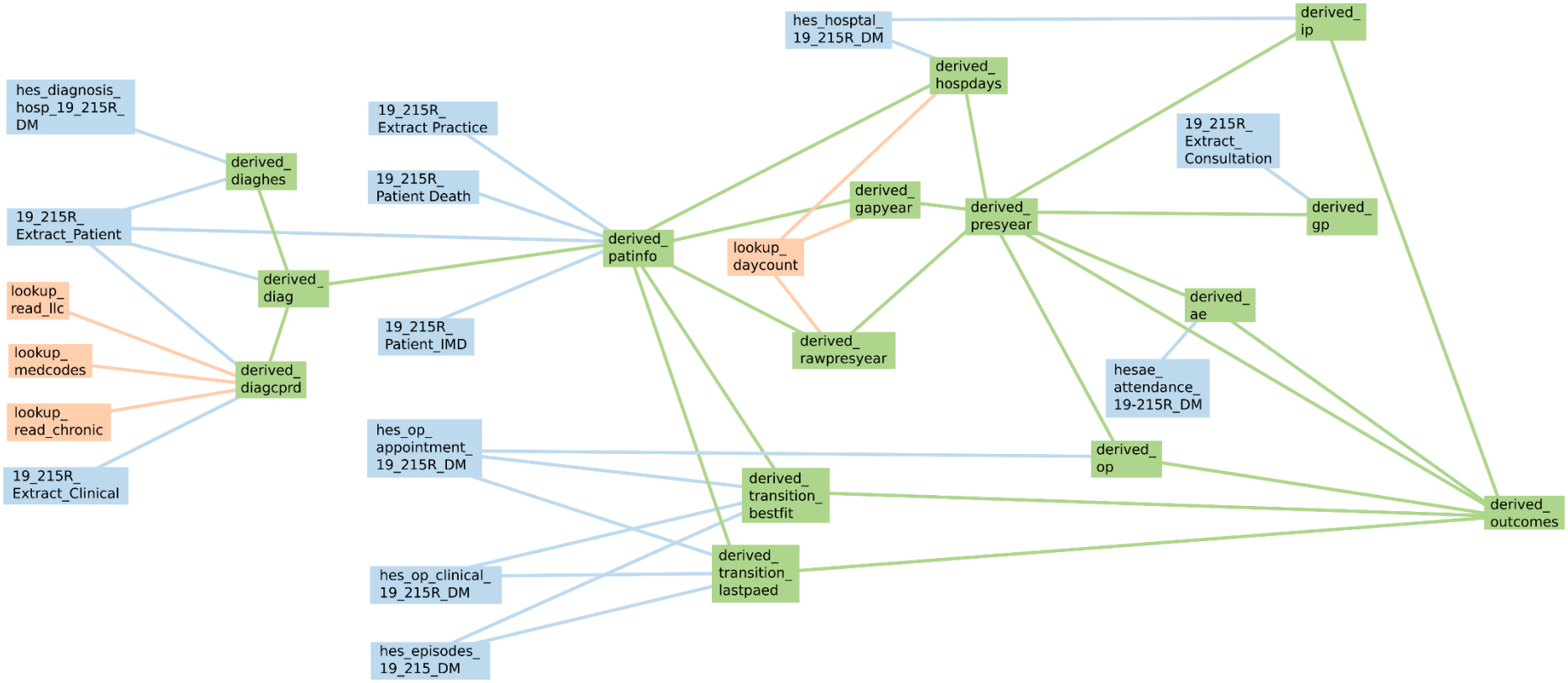
light green: derived tables previously created in the database

dark green: derived tables that are an output from the described process

A3.1.2 Overall schematic

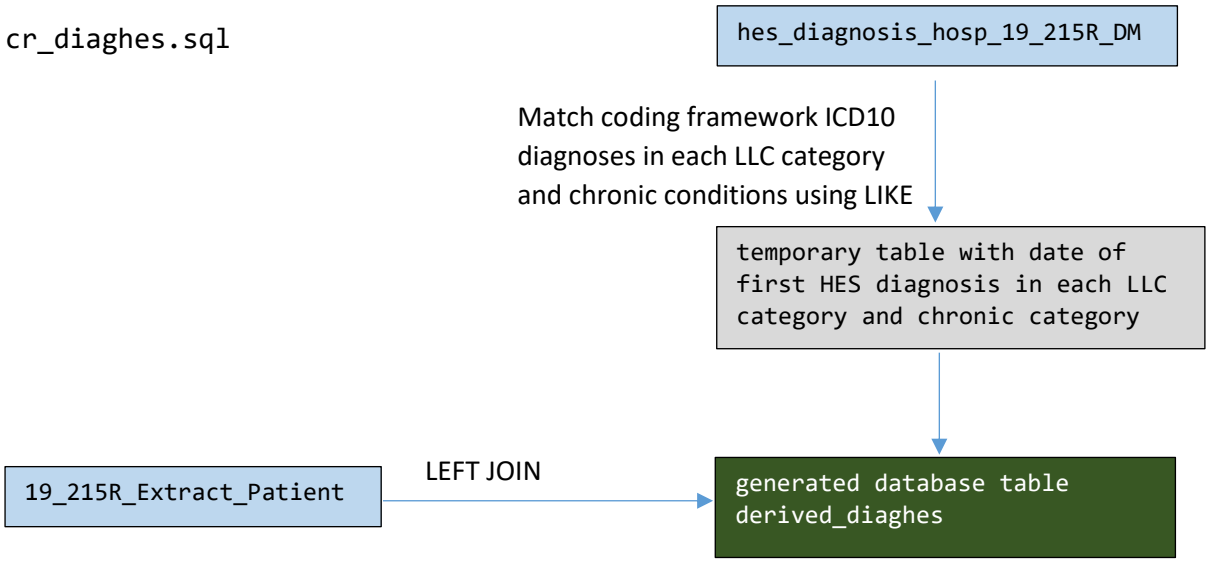
Diagram showing interactions between tables in original data and those created in the SQL database. All data flows are left to right.

24 SQL code files; 4639 lines of code.



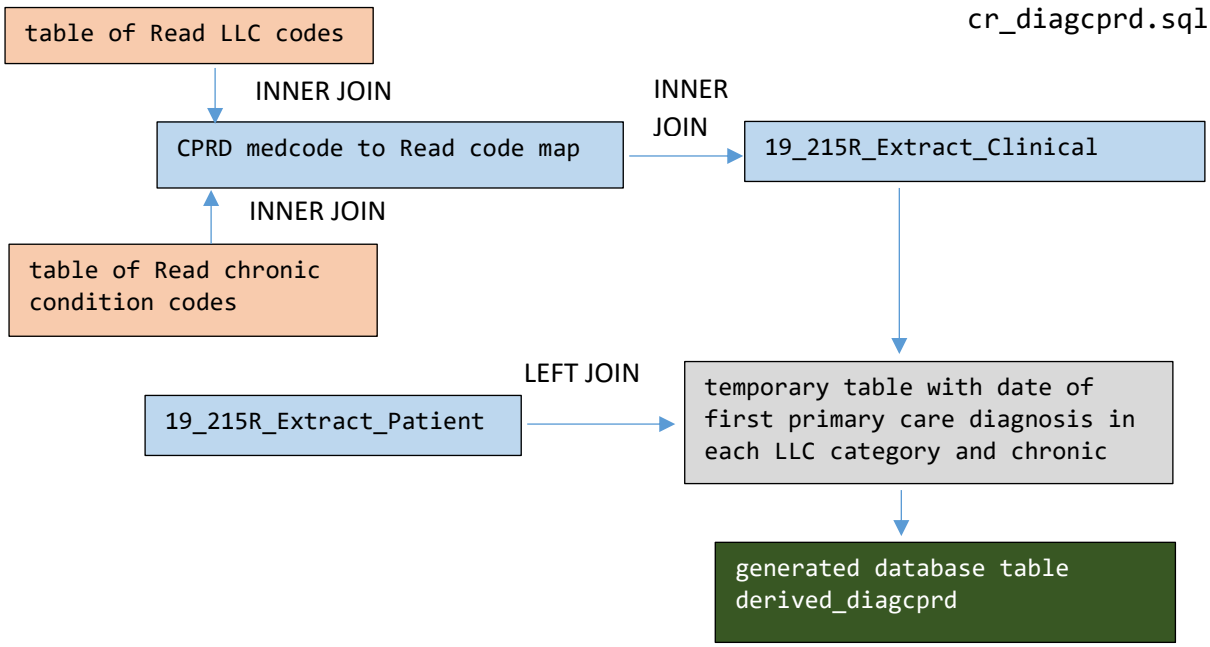
A3.1.3 Diagnosis matching for HES

Match lists of ICD10 diagnoses for LLC and chronic conditions. Based on GPCRPD cr_diag2.do, likely ported to SQL (similar to approach for paediatric neurology project). Uses LIKE for partial matching



A3.1.4 Diagnosis matching for CPRD

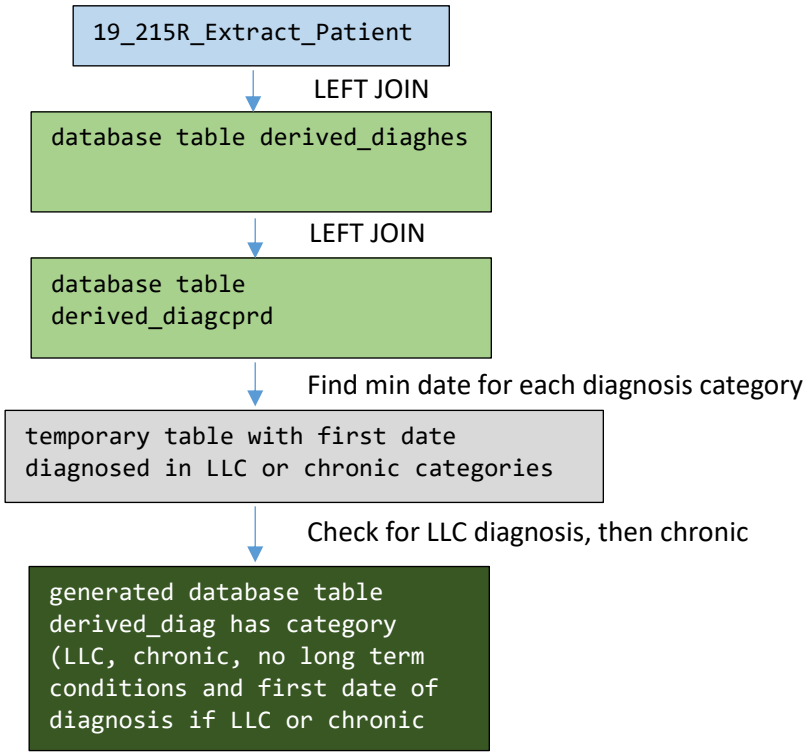
Similar to approach for HES, but Read codes are exact matched via medcodes so quicker (in code and running) to do joins rather than pattern matching.



A3.1.5 Determine combined grouping and first diagnosis dates

Find first date for each category of LLC diagnosis and chronic diagnosis - start with patient list and left join the derived_diaghes and dervied_diagcprd tables. Categorise hierarchically as LLC, chronic condition or no known long term condition individuals.

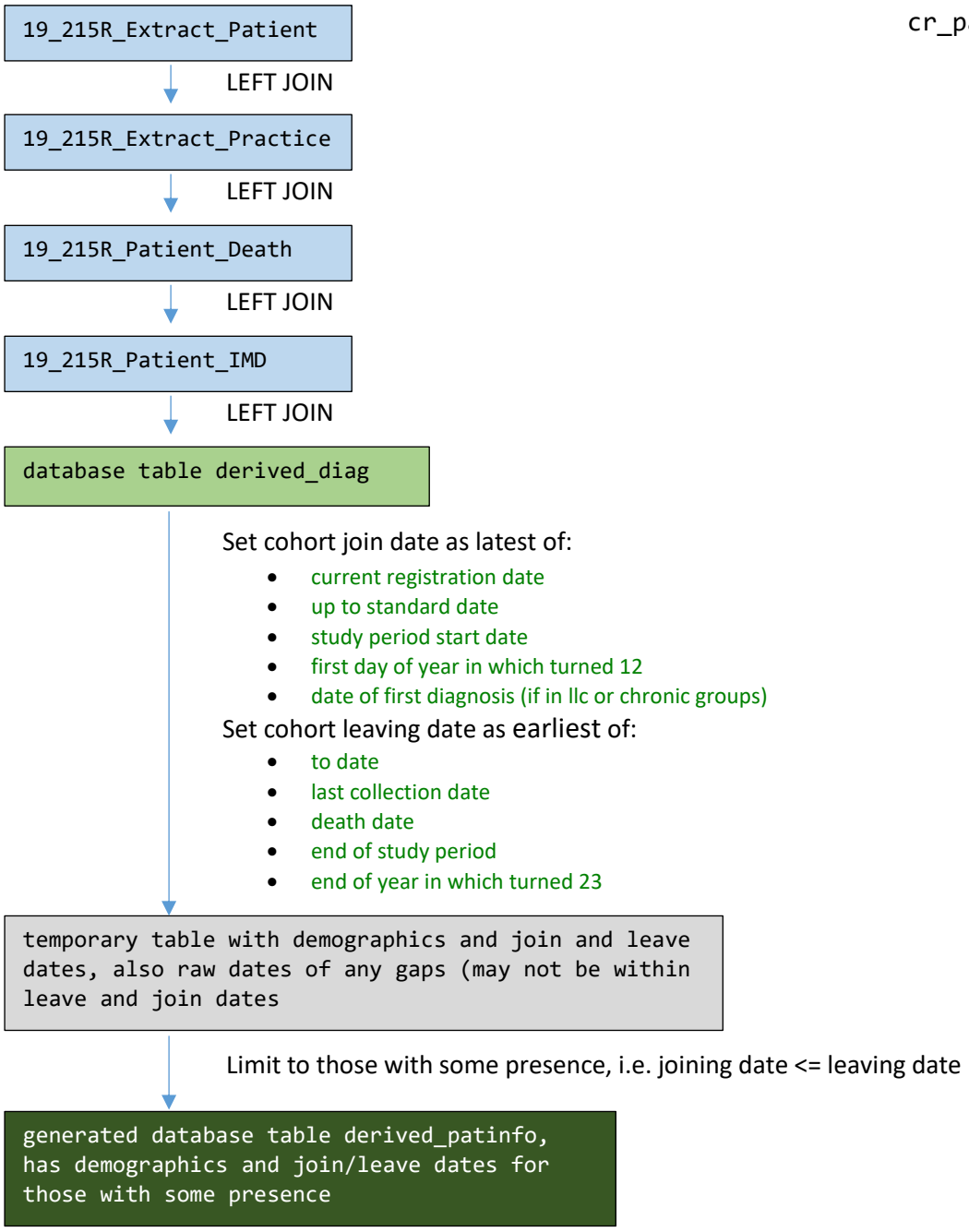
`cr_diag.sql`



A3.1.6 Determine patient characteristics and basic presence

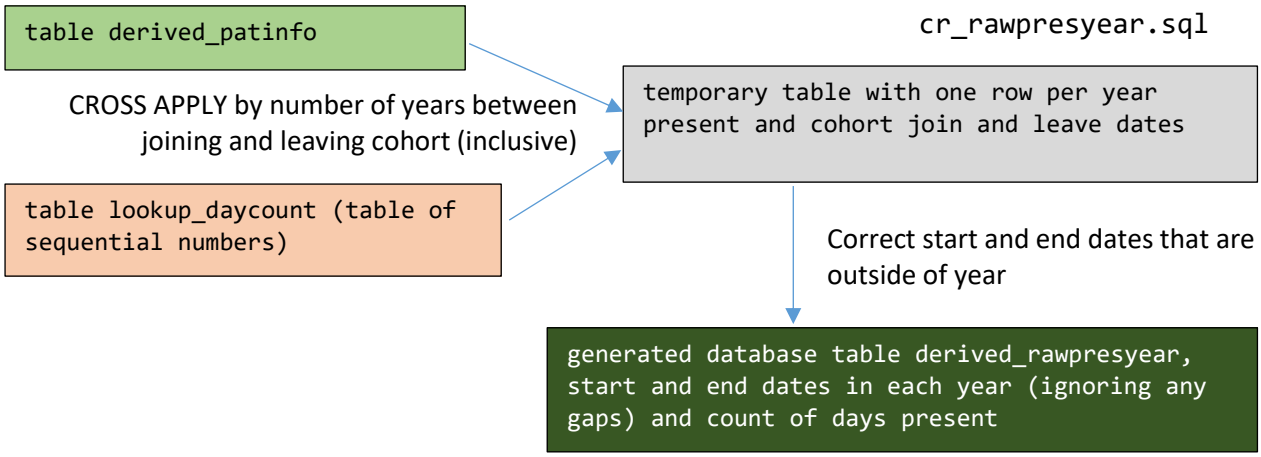
Determine basic demographics (age in each year, deprivation category, sex, ethnic group) and also start and end of presence in cohort (gaps in registration are analysed separately.

cr_patinfo.sql



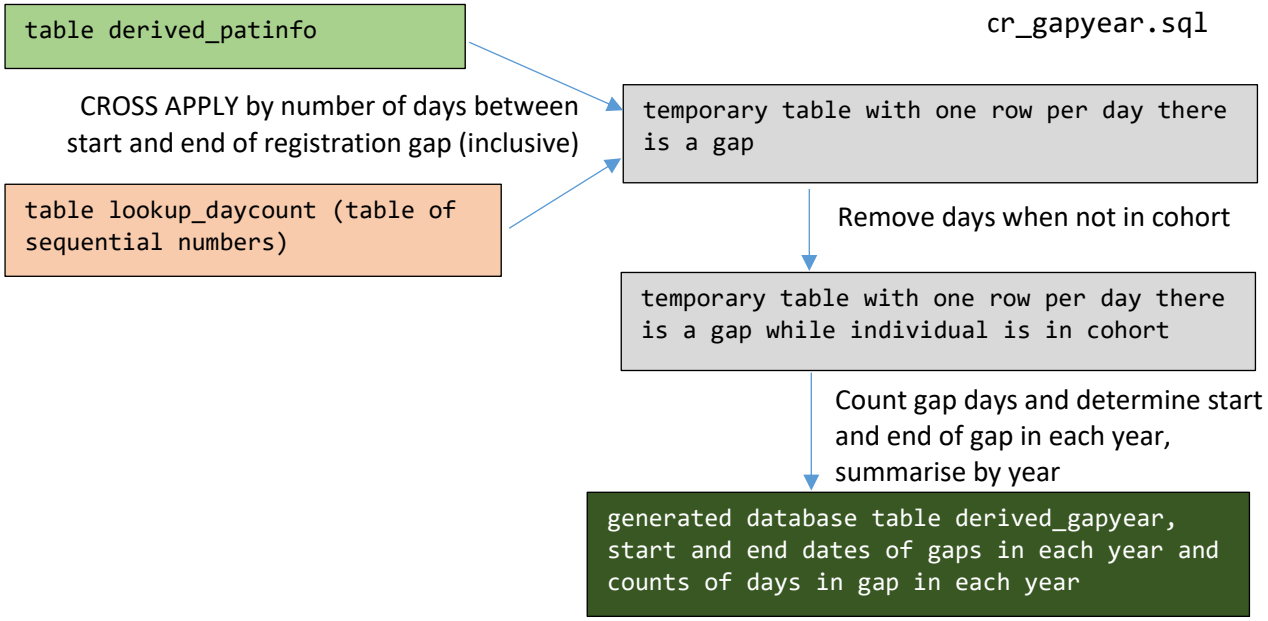
A3.1.7 Determine raw presence by year

Determine basic presence on a yearly basis, only taking account of joining and leaving dates, not yet gaps. Expand to add one row per person per year present.



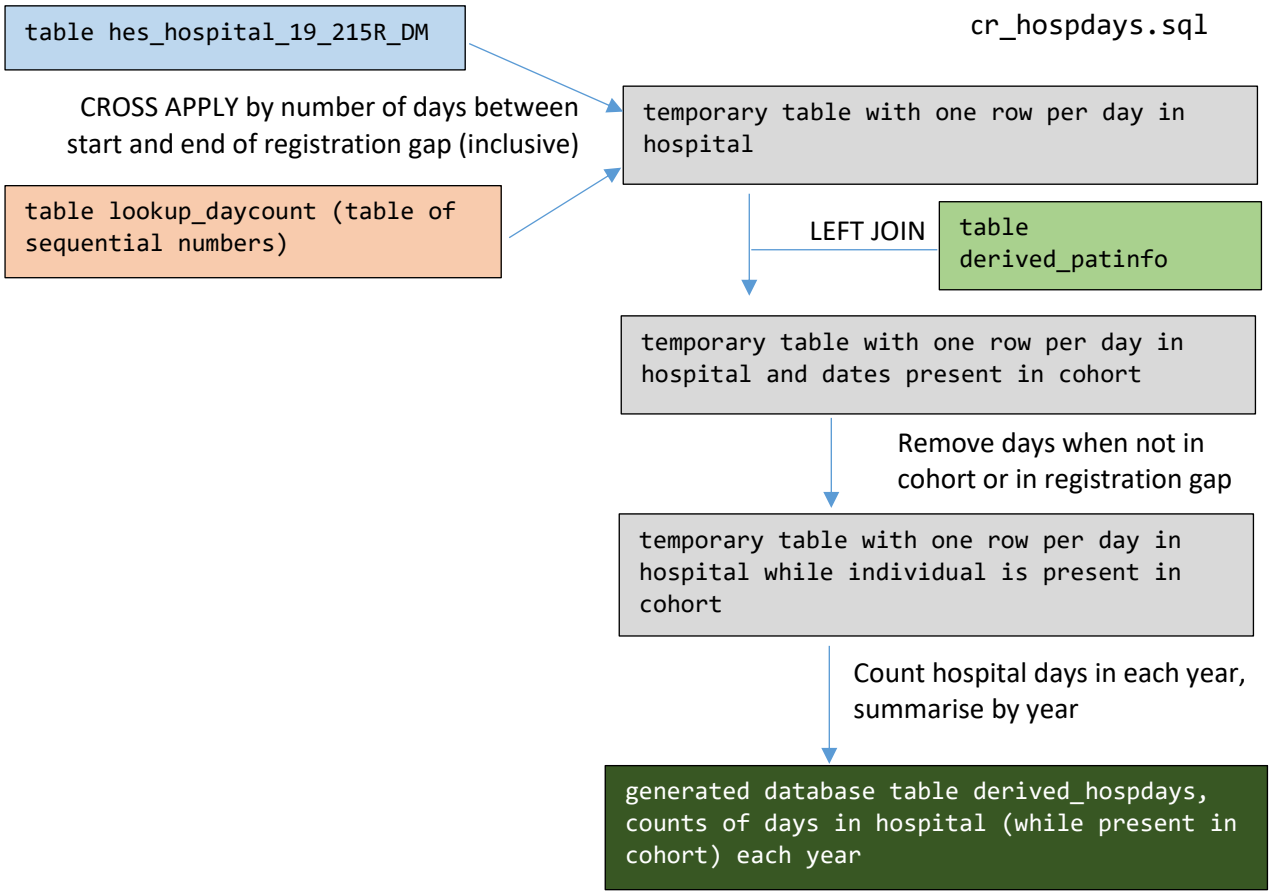
A3.1.8 Determine registration gaps by year

Take the raw information on registration gaps, expand to add a row for every day of a gap for each person, then delete rows that are not within the present in cohort period determined in cr_patinfo.sql. The count up rows to get number of gap days in each year and the start and end dates of gaps in each year and group by year to summarise.



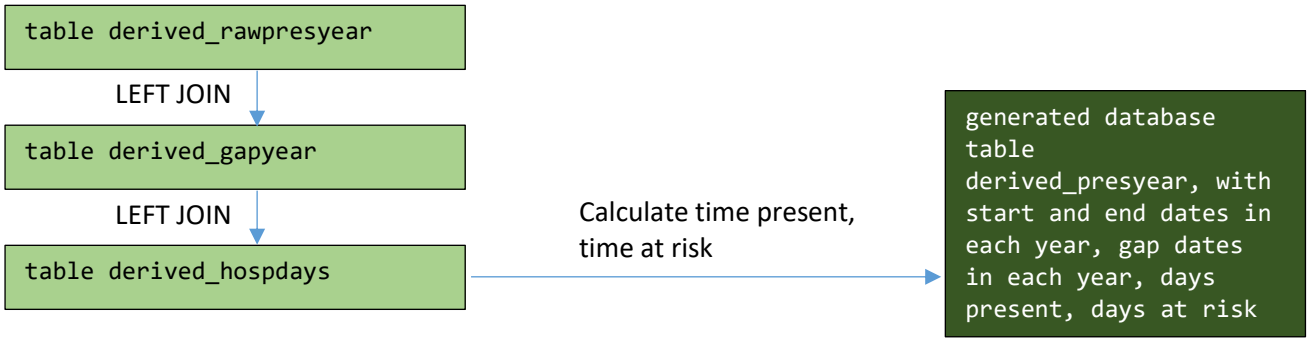
A3.1.9 Determine time in hospital each year

For some outcomes (A&E visit, inpatient admission) an individual is not at risk if they are already a hospital inpatient - determining time in hospital is needed for this and also required to calculate bed days per year. Hospital day data are loaded, expanded so that there is a row for each day in hospital and then days are removed when the individual was not in the cohort (before entry to cohort, after exit from cohort or in a registration gap). Days in hospital are then counted by year.



A3.1.10 Determine presence by year with time at risk

LEFT JOIN derived_rawpresyear to derived_gapyear and derived_hospyear, subtract gap days from raw time present to get time present in year, further subtract days in hospital to get time at risk (of outcome that cannot occur while in hospital).



A3.1.11 Determine transitions from paediatric to adult care

There are several potential approaches.(Shulman et al., 2020) Age based approaches are rejected as there is at least anecdotal evidence of transition ages varying widely. Therefore, categorisation of records will be used to determine transition for life limited and chronic condition groups.

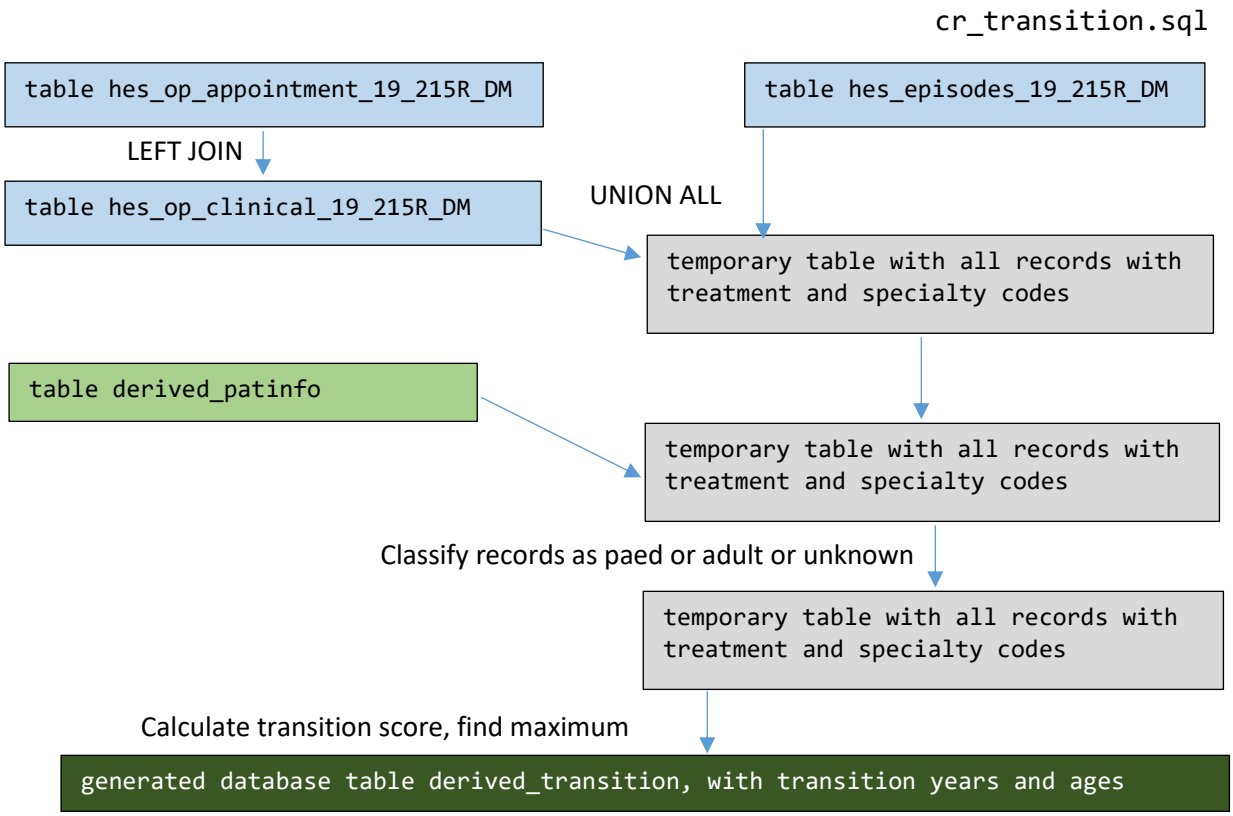
Each inpatient and outpatient record will be categorised as paediatric or adult based, based on the - records will be classified as paediatric is matching a paediatric specialty code. Where there is conflict between treatment main specialty and consultant main specialty, treatment main specialty takes precedence.

The core approach to be used here is to find the point that maximises percentage of overall episodes that are classified as paediatric before the transition point and adult after the transition point. If an individual has *N* records then for each record, *j*, the following calculation is made with records in ascending date order, in which *paed* is 1 for a record classified as paediatric and 0 otherwise and *adult* is 1 for a record classified as adult and 0 otherwise:

$$Transition\ score = 100 \times \frac{\sum_{i=1}^{j-1} paed + \sum_{i=j+1}^{N} adult}{N-1}$$

The transition point is the record with highest transition score. If there are ties then the mean date of the tied records is taken as the transition point.

Other approaches include setting transition as the first adult record or last paediatric episode (or the first/last with the same category of episode immediately after/before) or to define a transition period between paediatric and adult care, which runs from the first adult record to the last paediatric record. These alternative approaches will be used in sensitivity analyses, so also computed.



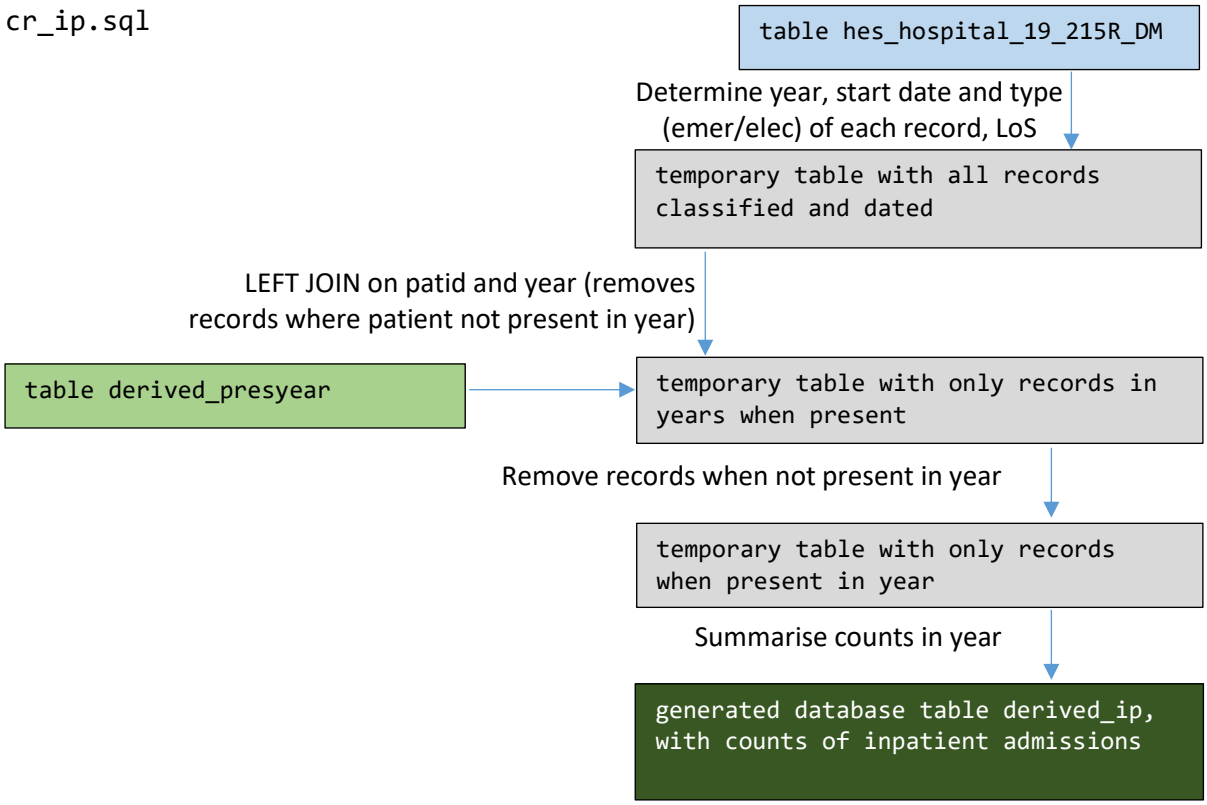
A3.1.12 Determine outcomes

General approach - take source outcome file, retain only records when present and count up per year per person.

Inpatient admissions

Count number of admissions, total and split by elective and emergency

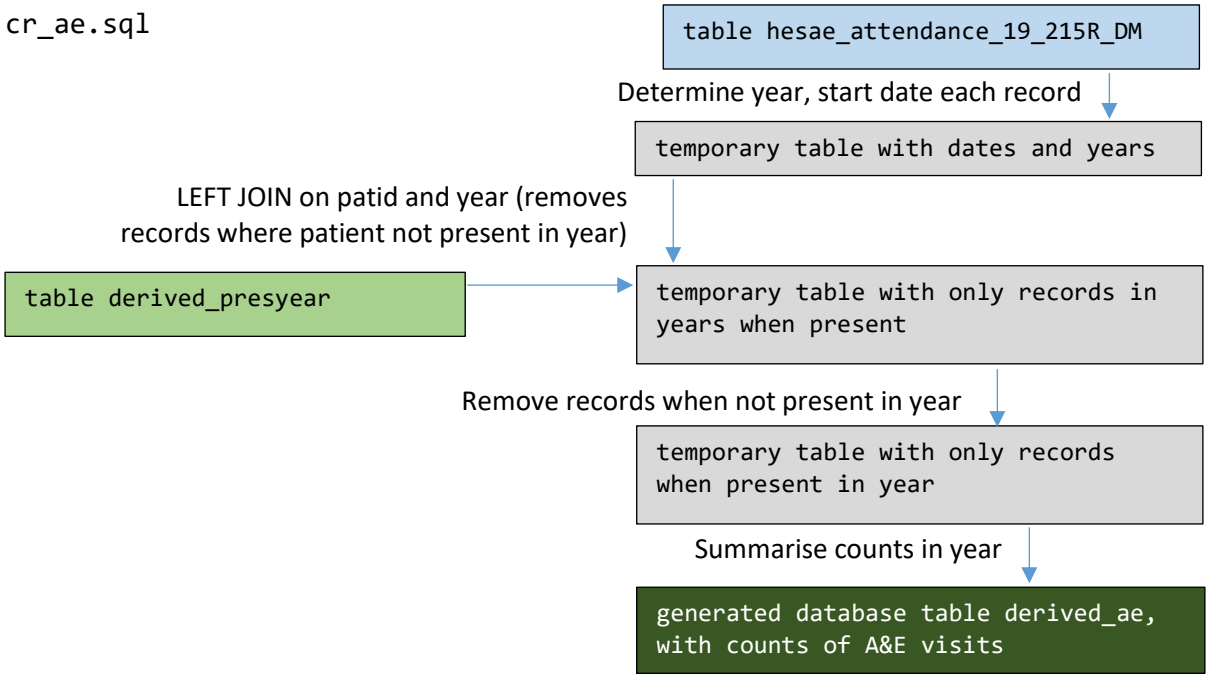
`cr_ip.sql`



A&E visits

Same approach as admissions, but no need to sub-classify.

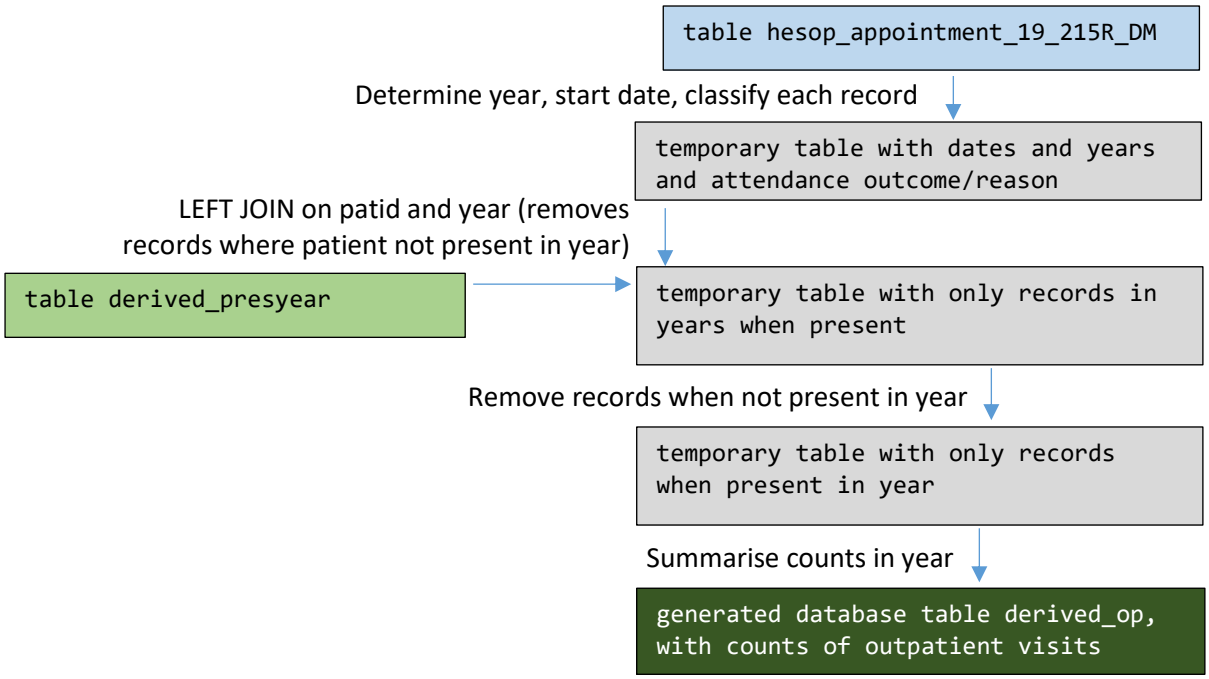
`cr_ae.sql`



Outpatient appointments

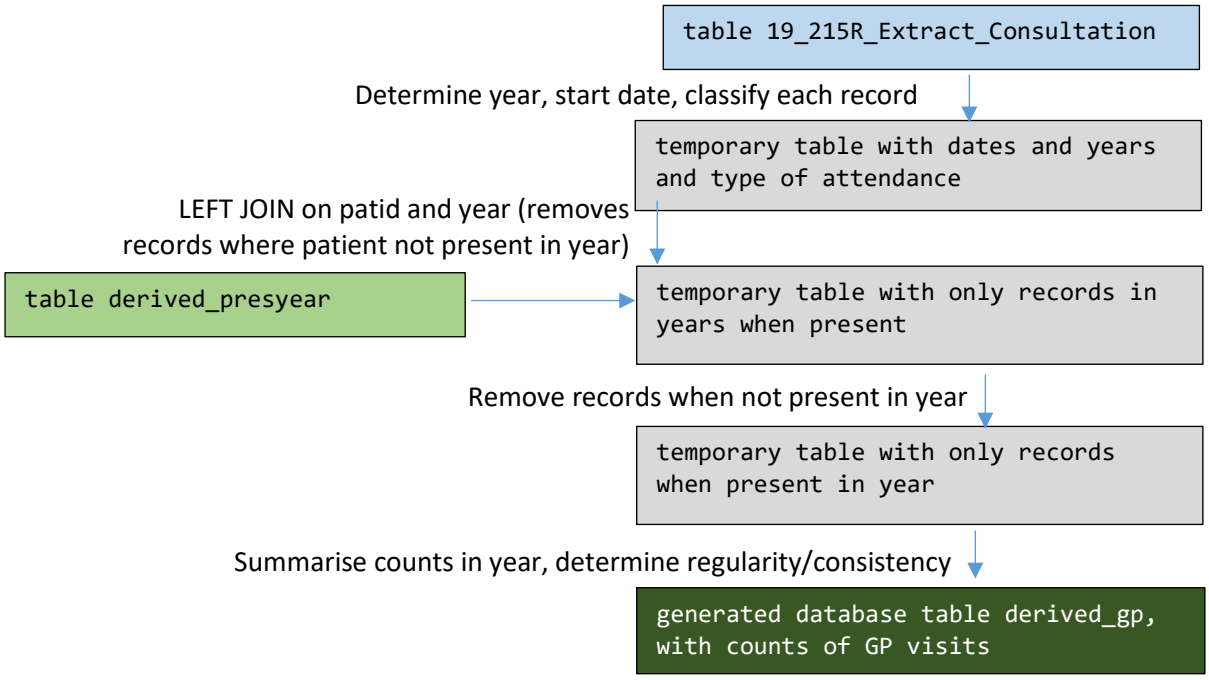
Similar to above, appointments classified as attended or not, with reasons for non-attendance.

`cr_op.sql`



GP contacts

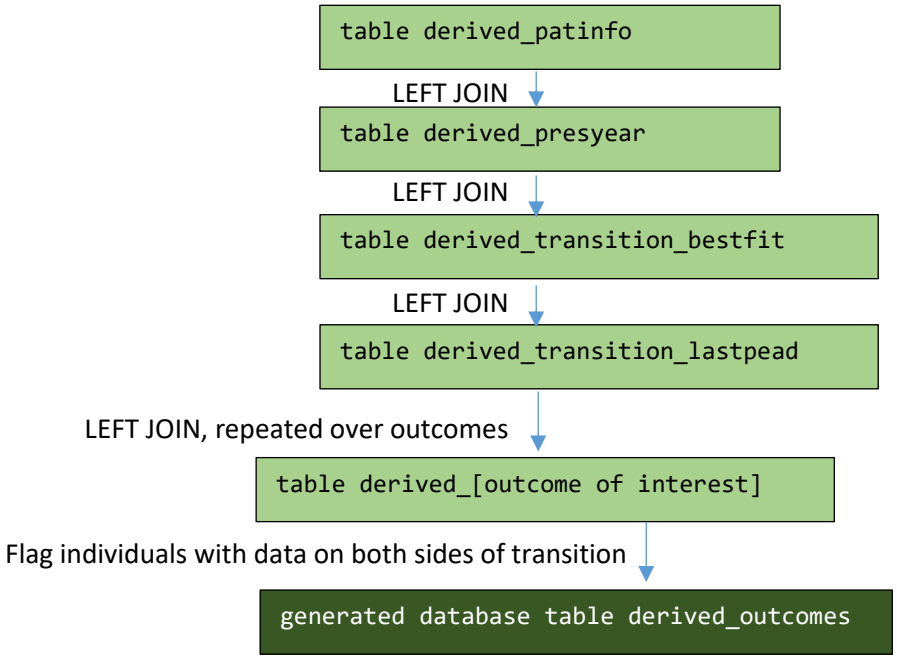
Similar to above, include classifications of contact types and calculate consistency and regularity in addition to frequencies.



A3.1.13 Table demographics, time at risk and outcomes

Brings together demographics, presence and outcomes into a table to be used in the models (can be done on demand, but will be used a lot so makes sense to generate permanent table).

`cr_models.sql`



A3.2 Statistical analyses

A3.2.1 Cohort formation

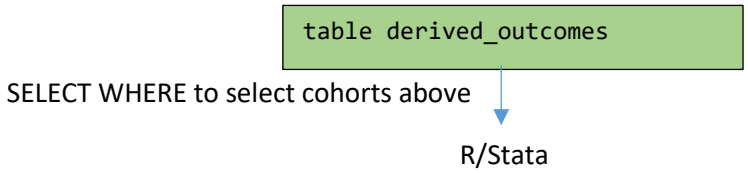
Generate, on demand, cohorts from the above table derived_outcomes, split by condition group (no long term conditions, chronic conditions and life limiting conditions) and with two cohort types:

1. All individuals
2. Only individuals with at least one year present before and after transition

The second condition is designed to test whether a cohort that transitions is different to a cohort including those that do not transition, e.g. due to death or due to delayed transition so that transition is not reached by the end of the study period (and also those too young to have transitioned by the end of the study period, for whom it is unknown whether they will transition on time, late or not at all).

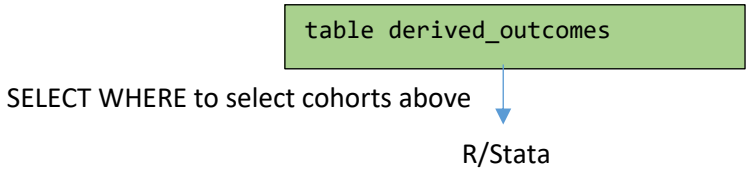
A3.2.2 Describe cohorts

Describe size, demographics and transition points in the different cohorts (LLC, chronic conditions, no long term conditions) and through time.



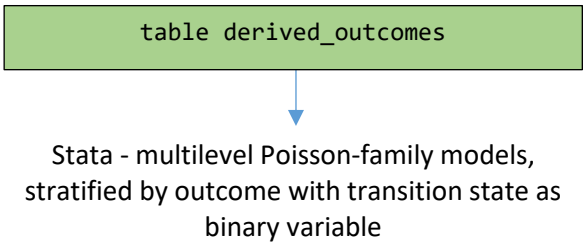
A3.2.3 Description of healthcare use

Describe use of outcomes (inpatient, planned and emergency; A&E; outpatient; GP contacts per person per year, by age, demographics and transition status.



A3.2.4 Transition healthcare use modelling

Multilevel Poison or negative binomial with age and transition status, possibly age at transition, stratified by condition groups. To be done for a cohort with data on both side of the transition Initially also run with transition fixed at age 16, as a further check



A3.3 References

SHULMAN, R., COHEN, E., BENCHIMOL, E. I. & NAKHLA, M. 2020. Methods for Measuring the Time of Transfer from Pediatric to Adult Care for Chronic Conditions Using Administrative Data: A Scoping Review. *Clinical Epidemiology,* 12**,** 691-698.