Multiple morbidity across the lifespan in people with Down syndrome or intellectual disabilities: a population-based cohort study using electronic health records

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Summary

Background The Down syndrome phenotype is well established, but our understanding of its morbidity patterns is limited. We comprehensively estimated the risk of multiple morbidity across the lifespan in people with Down syndrome compared with the general population and controls with other forms of intellectual disability.

Methods In this matched population-based cohort-study design, we used electronic health-record data from the UK Clinical Practice Research Datalink (CRPD) from Jan 1, 1990, to June 29, 2020. We aimed to explore the pattern of morbidities throughout the lifespan of people with Down syndrome compared with people with other intellectual disabilities and the general population, to identify syndrome-specific health conditions and their age-related incidence. We estimated incidence rates per 1000 person-years and incidence rate ratios (IRRs) for 32 common morbidities. Hierarchical clustering was used to identify groups of associated conditions using prevalence data.

Findings Between Jan 1, 1990, and June 29, 2020, a total of 10 204 people with Down syndrome, 39 814 controls, and 69 150 people with intellectual disabilities were included. Compared with controls, people with Down syndrome had increased risk of dementia (IRR 94·7, 95% CI 69·9–128·4), hypothyroidism (IRR 10·6, 9·6–11·8), epilepsy (IRR 9·7, 8·5–10·9), and haematological malignancy (IRR 4·7, 3·4–6·3), whereas asthma (IRR 0·88, 0·79–0·98), cancer (solid tumour IRR 0·75, 0·62–0·89), ischaemic heart disease (IRR 0·65, 0·51–0·85), and particularly hypertension (IRR 0·26, 0·22–0·32) were less frequent in people with Down syndrome than in controls. Compared to people with intellectual disabilities, risk of dementia (IRR 16·60, 14·23–19·37), hypothyroidism (IRR 7·22, 6·62–7·88), obstructive sleep apnoea (IRR 4·45, 3·72–5·31), and haematological malignancy (IRR 3·44, 2·58–4·59) were higher in people with Down syndrome, with reduced rates for a third of conditions, including new onset of dental inflammation (IRR 0·88, 0·78–0·99), asthma (IRR 0·82, 0·73–0·91), cancer (solid tumour IRR 0·78, 0·65–0·93), sleep disorder (IRR 0·74, 0·68–0·80), hypercholesterolaemia (IRR 0·69, 0·60–0·80), diabetes (IRR 0·59, 0·52–0·66), mood disorder (IRR 0·55, 0·50–0·60), glaucoma (IRR 0·47, 0·29–0·78), and anxiety disorder (IRR 0·43, 0·38–0·48). Morbidities in Down syndrome could be categorised on age-related incidence trajectories, and their prevalence clustered into typical syndromic conditions, cardiovascular diseases, autoimmune disorders, and mental health conditions.

Interpretation Multiple morbidity in Down syndrome shows distinct patterns of age-related incidence trajectories and clustering that differ from those found in the general population and in people with other intellectual disabilities, with implications for provision and timing of health-care screening, prevention, and treatment for people with Down syndrome.

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See Online for appendix

Introduction

Down syndrome is caused by the triplication of chromosome 21 (HSA21) and is the most commonly occurring aneuploidy in humans.[1,2] The characteristic phenotype associated with trisomy 21 has been well documented, with systemic changes in metabolic, immune, haemopoietic, and endocrine pathways. Some of these variations are directly related to the overexpression of genes on chromosome 21, whereas others may be secondary to a genome-wide dysregulation resulting from the presence of HSA21.[3] Trisomy 21 is syndromic and people with Down syndrome have a range of physical health morbidities,[4,5] which varies among the population. Similarly, although Down syndrome is usually associated with some level of intellectual disability, this varies from mild to severe and profound.[6]

Despite recognition that people with Down syndrome are at a higher risk of developing certain health conditions, research that investigates the incidence of conditions over their lifespan, or how morbidities relate to each other, is

Research in context

Evidence before this study

We undertook a literature search in Scopus for studies exploring morbidities in Down syndrome across the lifespan published in English until Nov 6, 2022. The search terms were ("Down* syndrome" OR "trisomy 21") AND (health* OR morbidity OR morbidities) AND (lifespan*) AND ("general population") AND ("intellectual disability" OR "learning disability"). Although there were many studies examining specific health conditions in either adults or children, we found no studies that examined the unique patterns of morbidities found in Down syndrome across the lifespan compared to the general population and people with other forms of intellectual disability, and we also found an acknowledged absence of evidence to support guidance for health surveillance of people with Down syndrome.

Added value of this study

There were several novel aspects to the present study. To our knowledge, this study was the first and largest study to date to examine the risk of new onset of a comprehensive range of several morbidities across the lifespan in Down syndrome compared to the general population and other forms of intellectual disability. We showed that new onset of morbidities follows age-related trajectories in people with Down syndrome and in those with other forms of intellectual disability and in the general population, with some unique patterns in Down syndrome. In particular, people with Down syndrome had an increased prevalence of developmentally associated conditions, evidence of accelerated ageing, and several morbidities associated with Alzheimer's disease. Prevalence data used for clustering analysis showed how health conditions clustered together, with with fewer clusters in people with Down syndrome. Cardiovascular risk factors and age-related diseases in particular were strongly clustered in Down syndrome, whereas in people with other forms of intellectual disabilities and general population controls, these conditions were spread across clusters.

Implications of all the available evidence

Health monitoring should be tailored to meet the specific needs of people with Down syndrome, to encompass both general health advice in optimising long-term health and syndrome-specific risks, which is different from patients with other intellectual disabilities in terms of both conditions to monitor for and timing of assessments. Our findings will help to update guidance and to plan targeted health provisions for people with Down syndrome.

scarce. Knowledge of the pattern of health conditions in people with Down syndrome and how this compares to the general population and those with other intellectual disabilities is vital to inform the development of preventive lifestyles and medical interventions, and to improve care for people with Down syndrome. Given that some conditions, such as Alzheimer's disease, occur at a much younger age in people with Down syndrome than in the general population, a better understanding of morbidities throughout life will help create targeted health-care guidance for different age groups. In addition, we could gain insight into underlying biological mechanisms that might link comorbidities and generate hypotheses for future research.

We aimed to explore the natural history of morbidities throughout the lifespan of people with Down syndrome compared with other people with intellectual disabilities and the general population. We sought to identify syndrome-specific health conditions and their age-related incidence, and potentially provide insights into the underlying genetic predisposition driving unique patterns and clustering of conditions.

Methods

Study design, setting, and participants

In this matched population-based cohort-study design, we used data from Jan 1, 1990, to June 29, 2020, extracted from the UK Clinical Practice Research Datalink (CPRD) GOLD database. CPRD GOLD is one of the world's largest datasets consisting of anonymised primary-care electronic-health records from family practices across the UK. CPRD GOLD data have been collected prospectively since 1987 and have been included in many validation studies and substantive research reports. Data on diagnoses, symptoms, prescriptions, referrals, and tests are collected from participating CPRD GOLD practices using Vision software and Read codes. Read codes are a hierarchical clinical classification system commonly used in primary care systems in the UK to describe the condition of a patient (eg, symptoms, past family history, and diagnoses) during a consultation.[7,8] CPRD GOLD contains data on more than 20 million patients, 3 million of whom are currently registered.[9] Data on sex, age, and ethnicity are largely representative of the general population in the UK.[8] The high quality of CPRD GOLD data has been confirmed in many studies.[10]

All patients ever diagnosed with Down syndrome were identified from the July 6, 2020 release of CPRD GOLD using Read codes for Down syndrome or trisomy 21. We planned two analyses. First, to identify potential differences between people with Down syndrome and the general population, and thus inform adjustment of population-wide guidance and policies, such as cancer-screening. Control participants were selected from the list of all registered patients in the database of people without Down syndrome. Controls were matched on family practice, sex, year of birth, and calendar date of start of record, to within 1·5 years. Up to four controls were randomly sampled for each patient with Down syndrome using the sample function in the R program.

The matching algorithm employed the with-replacement approach. Our second analysis aimed to identify morbidities unique to Down syndrome (ie, genetic risk), which is independent of general health risks and treatment inequalities associated with intellectual disabilities; all patients with an intellectual disability diagnosis but without Down syndrome were included as a comparator group. The group with intellectual disabilities was unmatched given that it was not possible to match intellectual disabilities to patients with Down syndrome without reusing a substantial number of patients with intellectual disabilities. Therefore, Down syndrome and intellectual disability comparisons were whole-population comparisons. Midyear counts of patients and general practices for each group by study year are provided (appendix p 3). The protocol was approved by the CPRD Independent Scientific Advisory Committee (ISAC protocol 20-048R). Data were accessed and processed under the terms of King's College London multistudy licence; further information is available from CPRD and previous studies.[8] These analyses represent one component of a larger study done on behalf of the pan-European GO-DS21 Consortium.

Variables

Morbidities were identified from the clinical records of patients using Read codes. Read-code lists were created using a two-step verification process involving two reviewers (RAB and SEP) and a third reviewer (AS) if consensus was not met;[11] LFC also contributed as a third reviewer to some code lists (depending on the expertise required), and qualified senior clinicians discussed and agreed in study meetings whether there were any remaining issues (MCG, LFC, and AS). 33 morbidities covering health conditions associated with Down syndrome (integrating those deemed important to examine multimorbidity)[12] were included: congenital heart disease; dementia; hypothyroidism; epilepsy; obstructive sleep apnoea; haematological malignancy; cancer (solid tumour); chronic respiratory disease excluding asthma (including chronic obstructive pulmonary disease, pneumonia, and cystic fibrosis); asthma; obesity; cataract; glaucoma; peripheral vascular disease; thrombosis; ischaemic heart disease; stroke or cerebrovascular disease; diabetes (both type 1 and type 2); kidney disease; hypertension; hypercholesterolaemia; osteoporosis or osteopenia; inflammatory bowel disease; ear disorders; constipation; endocrine disorders; systemic autoimmune conditions; peripheral autoimmune conditions; dental inflammation; sleep disorders not including obstructive sleep apnoea; liver disease; mood disorder; anxiety; and psychosis (code lists are provided in the appendix pp 51–266).

Data source, bias, and study size

Data were extracted from CPRD GOLD, and the study size was determined by the number of people with Down syndrome and intellectual disabilities within the dataset. The sample size of general population controls was determined by matching up to four controls to people with Down syndrome. As the study used all available people with Down syndrome and intellectual disabilities within CPRD GOLD at the time of data extraction, potential sampling bias was minimised. Practice migration is captured in the last collection date variable in CPRD, which represents the last occasion on which data were collected from the practice. We included data from 885 family practices for people with Down syndrome and general population controls and 942 family practices for people with intellectual disabilities. Following usual practice in CPRD research, individual patient records were analysed up to which came earliest, end of registration, patient death date, or last data collection.

Statistical analysis

Each morbidity was considered to be present if recorded, and absent if otherwise not recorded. Rates of new diagnoses of morbidities people with Down syndrome, people with intellectual disabilities, and in general population controls were estimated using incidence rates per 1000 person-years; 95% CIs were derived from the Poisson distribution. Person-time was calculated between 1990 and 2020. Incidence across the lifespan was investigated by dividing age of diagnosis into the categories 0–4 years, 5–14 years, and 10-year age groups up to 75 years, and then calculating incidence rates for each age group. Incidence rates by age category for each morbidity were plotted and visually grouped together on the basis of their age-associated patterns of onset to better understand morbidity onset and identify morbidities that might develop at similar ages, with the Down syndrome group as the primary group of interest. Prevalence rates rather than incidence rates were calculated for congenital heart disease, given that congenital heart disease usually presents at birth. To estimate the incidence rate ratio (IRR) for morbidities between people with Down syndrome and controls, Poisson regression models were fitted and adjusted for age, calendar year, and sex. Age was fitted as a continuous predictor, with a quadratic term to allow for non-linearity; similarly, calendar year squared was fitted. Sex and Down syndrome status (Down syndrome and controls) were fitted as factors. Poisson regression models were also fitted for people with Down syndrome and those with intellectual disabilities to explore the pattern of Down syndrome-specific morbidities compared with other forms of intellectual disabilities. Because of the large dataset included in our study, any small difference might have been statistically significant; therefore we relied on CI estimation for interpretation. No adjustment was made for multiple comparisons.

To explore how groups of health morbidities cluster together, a multiple correspondence analysis (MCA)

	People with Down syndrome	General population controls	People with other intellectual disabilities
Number of individuals	10 204	39 814	69 150
Sex			
Male	4832 (47·4%)	19 133 (48·1%)	44 644 (64·6%)
Female	5372 (52·6%)	20 681 (51·9%)	24 506 (35·4%)
Median age in years at cohort entry (IQR)	26 (7–41)	23 (4–38)	19 (6–36)
Median length of follow-up in years (IQR)	7 (3–13)	10 (4–17)	6 (2–12)
Number of deaths during the study period	1224 (12·0%)	991 (2·5%)	4983 (7·2%)
Median number of patients per family practice	9	36	55
Number of patients registered within each region of family practices across the UK (%)			
Northeast England	307 (3·01%)	955 (2·40%)	1177 (1·70%)
Northwest England	1107 (10·85%)	4139 (10·40%)	6288 (9·09%)
Yorkshire and the Humber	269 (2·64%)	1053 (2·64%)	1617 (2·34%)
East Midlands	284 (2·78%)	1126 (2·83%)	2124 (3·07%)
West Midlands	841 (8·24%)	3319 (8·34%)	6505 (9·41%)
East of England	586 (5·74%)	2309 (5·80%)	4731 (6·84%)
Southwest England	912 (8·94%)	3538 (8·89%)	6863 (9·92%)
South central England	849 (8·32%)	3375 (8·48%)	7433 (10·75%)
London	935 (9·16%)	3704 (9·30%)	6525 (9·44%)
Southeast coast of England	736 (7·21%)	2919 (7·33%)	7459 (10·79%)
Northern Ireland	468 (4·59%)	1857 (4·66%)	1613 (2·33%)
Scotland	1706 (16·72%)	6743 (16·94%)	9390 (13·58%)
Wales	1204 (11·80%)	4777 (12·00%)	7425 (10·74%)

Table: **Demographic information of patients**

with agglomerative hierarchical clustering was done in the Down syndrome population, intellectual disabilities group, and the matched general population controls separately. The MCA used prevalence data from the most recent period of 2015 to 2020, with each morbidity coded as present or absent. The aim was to identify clusters of morbidities that were closely correlated among themselves and showed few correlations with other clusters. MCA has previously been used to analyse clustering of morbidities,[13,14] with MCA and clustering approaches that used similar data as the present study.[13] First, the MCA was done to determine the principal dimensions. The number of dimensions retained were based on the elbow of a scree plot. Next, variable coordinates calculated from the MCA were extracted and used to conduct agglomerative hierarchical clustering. Ward's minimum variance method was applied, which forms clusters with the total within-cluster variance minimised for each cluster.[15] The overall number of clusters was determined using the silhouette-plot method.[16] We used R version 4.1.3[17] for all data preparation and analyses. Reporting followed STROBE recommendations.

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Between Jan 1, 1990, and June 29, 2020, a total of 10 204 people with Down syndrome, 39 814 controls, and 69 150 people with intellectual disabilities were included (table). There were approximately the same number of male and female individuals in the Down syndrome group and control group, but a higher proportion of males than females in the group with intellectual disabilities. The group with intellectual disabilities were younger than controls and people with Down syndrome at cohort entry and exit. Population controls were followed up for longer than the two other groups, and a higher percentage of people with Down syndrome died during the study period than controls or those with intellectual disabilities. 66·90% of practices were registered in England for people with Down syndrome, 66·40% for controls, and 73·35% for people with intellectual disabilities (because of the sample size difference).

Congenital heart disease was more prevalent in Down syndrome (23·21%) than in people with intellectual disabilities (2·40%) and controls (0·67%).

In Down syndrome, incidence of asthma, obstructive sleep apnoea, haematological malignancy, and inflammatory bowel disease was higher in childhood and adolescence, with a consistent pattern of lower incidence with increasing age. Incidence of these conditions was generally higher in people with Down syndrome than in people with intellectual disabilities and controls; apart from asthma, which showed higher incidence in those with intellectual disabilities and controls than in people with Down syndrome. Incidence of haematological malignancy was higher at older ages in those with intellectual disabilities and control groups than in people with Down syndrome (figure 1; appendix pp 6–11).

Incidence increased with increasing age for cataracts, obesity, osteoporosis or osteopenia, kidney disease, and diabetes in all groups. In Down syndrome, incidence of these conditions began to increase at earlier ages than in the intellectual disabilities group and control group. The incidence of diabetes and obesity in Down syndrome was higher in younger age groups, but lower than in people with intellectual disabilities and controls in the older age groups (figure 1; appendix pp 6–11).

People with Down syndrome had higher rates of ear disorders, endocrine disorders, hypothyroidism, and peripheral autoimmune conditions throughout the lifespan than people with intellectual disabilities and controls (figure 1; appendix pp 6–11).

There were several morbidities that had lower incidence in people with Down syndrome. Hypercholesterolaemia, hypertension, ischaemic heart disease, solid tumour cancers, glaucoma, and mental health disorders were all lower in Down syndrome across the lifespan. Rates of psychosis increased in incidence at younger ages and remained high across the lifespan in those with intellectual disabilities than in those with intellectual

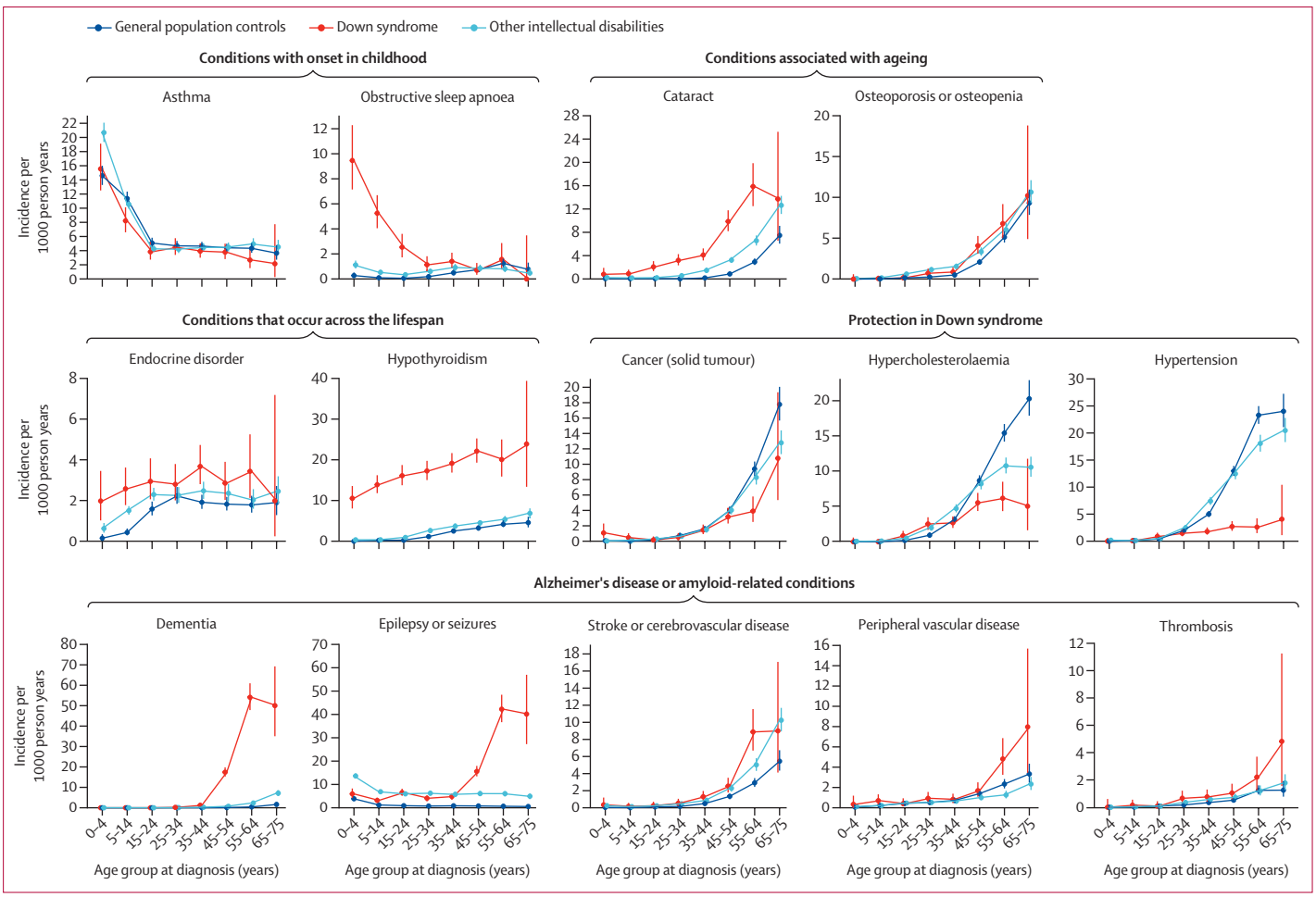

Figure 1: **Incidence rate groupings for morbidities across the lifespan in people with Down syndrome, people with intellectual disabilities, and general population controls**
Data are presented with 95% CIs. Red represents people with Down syndrome, light blue those with intellectual disabilities, and dark blue controls from the general population. Prototypical exemplars that represent each grouping of morbidities based on their incidence rates across the lifespan for people with Down syndrome, people with intellectual disabilities, and controls are presented (appendix pp 6–11 for all groupings; data for all figures can be found in the appendix pp 19–50).

disabilities compared to those with Down syndrome and controls (figure 1).

Incidence of liver disease, systemic autoimmune conditions, and dental inflammation followed similar age-related patterns across the three groups, but with some differences. Dental inflammation rates were higher in people with Down syndrome and intellectual disabilities than in controls across the lifespan. Both chronic respiratory disease and constipation showed a U-shaped-curve pattern in Down syndrome; rates were high in childhood and lower throughout adolescence and adulthood, with incidence increasing after age 30 years (appendix p 11).

The most notable IRR for people with Down syndrome was dementia, which was nearly 95 times as high as the IRR for controls (figure 2). New onset of hypothyroidism, epilepsy, cataract, obstructive sleep apnoea, haematological malignancy, and chronic respiratory disease were significantly more frequent in Down syndrome, ranging from an IRR of 10·63 (9·60–11·77) for hypothyroidism to 4·11 (3·69–4·59) for chronic respiratory disease. In people with Down syndrome, the rate of new onset of kidney disease was more than 3·5 times as high as the rate among controls, whereas the rates of constipation and cerebrovascular disease in Down syndrome were more than 2·5 times as high. IRRs for thrombosis, psychosis, obesity, and peripheral autoimmune conditions in Down syndrome were twice as high as the rates in controls. New onset of endocrine disorders, ear disorders, peripheral vascular disease, inflammatory bowel disease, osteoporosis or osteopenia, sleep disorders (not including obstructive sleep apnoea), dental inflammation, and diabetes were significantly higher in Down syndrome than in controls, ranging from an IRR of 1·86 (1·60–2·16) in endocrine disorders to 1·19 (1·05–1·36) in diabetes (figure 2).

However, asthma, cancer (solid tumours), hypercholesterolaemia, ischaemic heart disease, and common

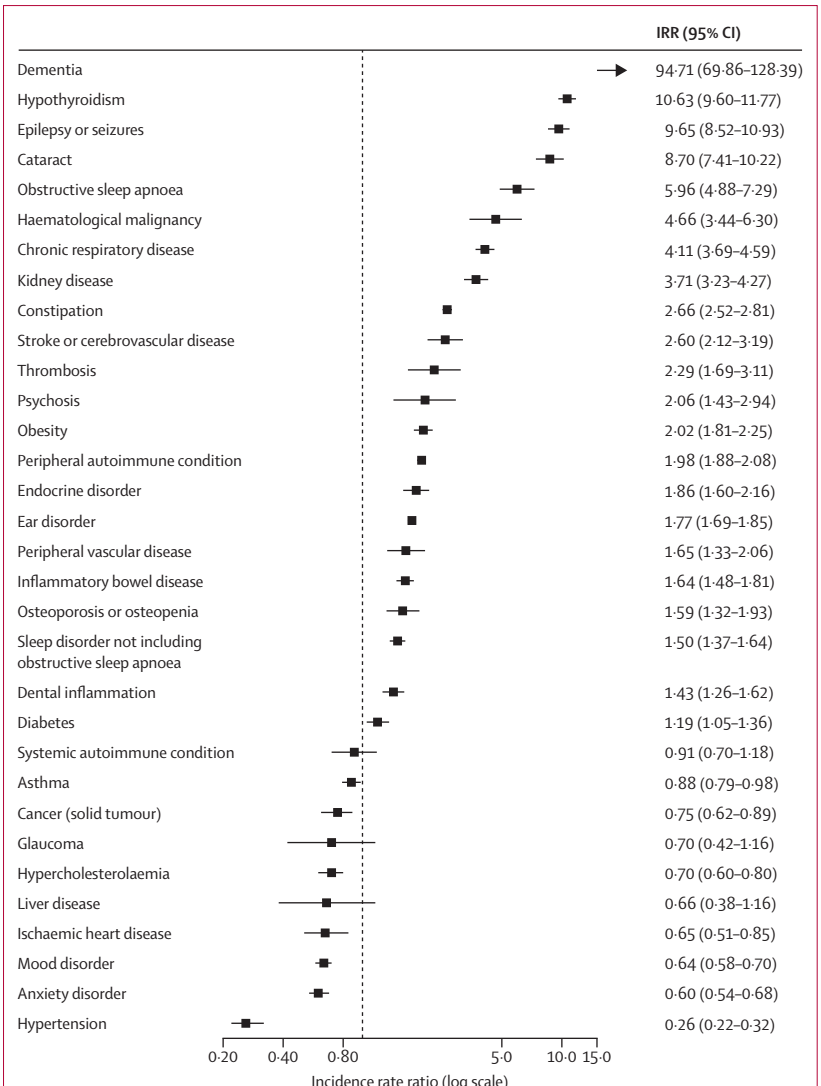

Figure 2: **Poisson regression models between people with Down syndrome and general population controls**
IRRs were adjusted for each of the diagnoses shown. IRR=incidence rate ratio.

mental health disorders (mood disorders and anxiety disorders) were significantly less common in Down syndrome than in controls. New onset of hypertension was particularly less frequent in Down syndrome with an IRR of 0·26 (0·22–0·32). There was no statistically significant difference in rates of systemic autoimmune conditions, glaucoma, or liver disease between people with Down syndrome and controls (figure 2).

The dementia IRR among people with Down syndrome was 16·60 times higher (95% CI 14·23–19·37) than in people with intellectual disabilities, and hypothyroidism was 7·22 times as high (6·62–7·88) in Down syndrome (appendix p 12). New onset of obstructive sleep apnoea, haematological malignancy, and cataract were 4·5 times to three times higher in people with Down syndrome than in those with intellectual disabilities, whereas rates of chronic respiratory disease, peripheral vascular disease, and kidney disease were twice as high in Down syndrome. In Down syndrome, thrombosis, peripheral autoimmune conditions, inflammatory bowel disease, epilepsy, stroke and cerebrovascular disease, ear disorders, constipation, and endocrine disorders were significantly more common than in those with intellectual disabilities, with an IRR ranging from 1·58 (1·17–2·13) for thrombosis to 1·18 (1·02–1·36) for endocrine disorders.

The incidence for approximately a third of morbidities was lower in people with Down syndrome than in those with intellectual disabilities. These morbidities included new onset of dental inflammation, osteoporosis or osteopenia, asthma, cancer (solid tumour), sleep disorders, hypercholesterolaemia, diabetes, mood disorders, glaucoma, and anxiety disorders. The hypertension (IRR 0·26, 0·22–0·32) and psychosis (IRR 0·23, 0·17–0·31) rates among people with Down syndrome were significantly lower than in those with intellectual disabilities. There were no significant differences in the rates of systemic autoimmune condition, obesity, ischemic heart disease, and liver disease.

There were four clusters of co-occurring types of morbidities within the Down syndrome sample (silhouette width 0·62). The largest, cluster 1, consisted of 16 morbidities that are commonly associated with Down syndrome, including congenital heart disease, dementia, epilepsy, hypothyroidism, obesity, and obstructive sleep apnoea (syndromic conditions). Cluster 2 consisted of 11 long-term morbidities with a distinct cardiovascular disease profile, including hypertension, ischaemic heart disease, cardiovascular disease, and peripheral vascular disease. Cluster 3 consisted of morbidities that might have an autoimmune cause, and cluster 4 comprised mental health morbidities (figure 3).

There were ten clusters in people with intellectual disabilities (silhouette width 0·59), and seven clusters in the general population (silhouette width 0·67; appendix p 13). There were some similarities. A set of conditions from cluster 1 in people with Down syndrome showed overlap with clusters in people with intellectual disabilities and controls, with asthma, constipation, inflammatory bowel disease, and ear disorders grouped together. Cluster 6 in the general population was the same as cluster 3 in Down syndrome, and was similar to cluster 3 in people with intellectual disabilities. However, in the general population and the intellectual disabilities group, cardiovascular morbidities and age-related diseases were spread across more clusters than in Down syndrome. In general, the control and intellectual disabilities groups had similar clustering, although differences were observed. Clustering of cardiovascular risk factors, including hypertension, diabetes, and hypercholesterolaemia was similar in people with intellectual disabilities and controls. However, in people with intellectual disabilities, obesity clustered with

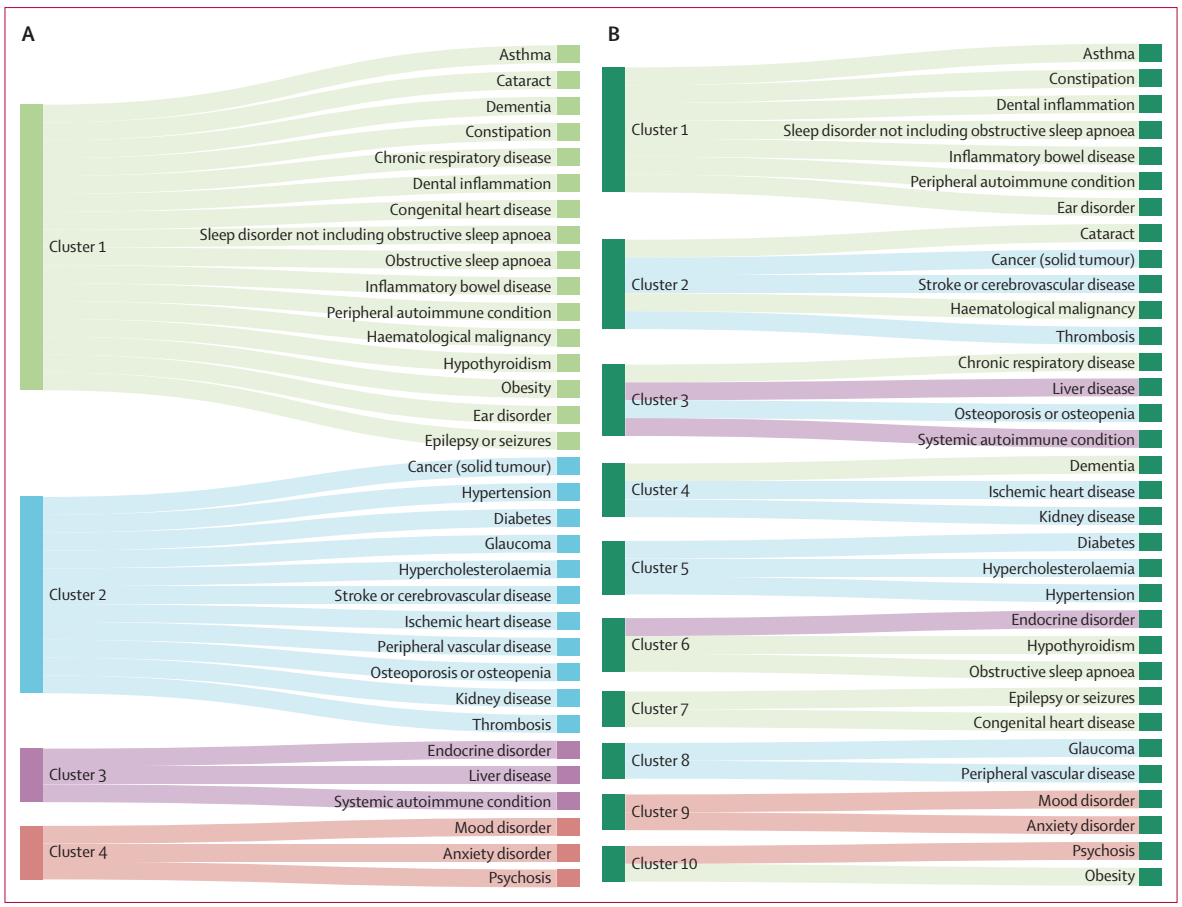

Figure 3: **Hierarchical clustering of health conditions in people with Down syndrome (A) and people with intellectual disabilities (B)**
Clusters for people with intellectual disabilities were colour coded on the basis of the clustering of health conditions in the Down syndrome sample to illustrate differences in clusters of conditions between people with intellectual disabilities and Down syndrome. There was no hierarchical significance to the order of the conditions within each cluster.

psychosis, whereas obstructive sleep apnoea clustered with hypothyroidism and other endocrine disorders. Epilepsy clustered with congenital heart disease in people with intellectual disabilities but not in controls, possibly because these morbidities often co-occur in genetic and congenital syndromes in people with intellectual disabilities.

Discussion

Across the lifespan, people with Down syndrome have a varied incidence of multiple morbidity, broadly related to age-associated trajectories. These conditions include those with onset in childhood, those associated with ageing, conditions that are common across the whole lifespan, and those which might be Alzheimer's disease or amyloid related. The incidence for conditions in Down syndrome were similar to those found in previous literature for conditions that are well established as being more common in Down syndrome (eg, dementia and hypothyroidism);[1,5,18] in addition, we provided IRRs in comparison with both the general population and other individuals with intellectual disabilities, comparisons which are currently scarce in the literature (including for conditions not previously recognised as being common in Down syndrome, such as kidney disease). We confirmed that some conditions show reduced risk in Down syndrome, such as hypertension and mental health conditions,[5] and identified specific conditions that people with Down syndrome are at an increased risk of compared with people with intellectual disabilities (eg, obstructive sleep apnoea and haematological malignancy), and conditions with higher incidence in people with intellectual disabilities than in those with Down syndrome (eg, psychosis). These findings allow for a better understanding of how multiple morbidity in Down syndrome differs from other forms of intellectual disabilities, a distinction that has largely been overlooked in the literature.

We identified several conditions that increased in incidence alongside dementia, including late-onset epilepsy and seizures and cerebrovascular disease, which

are often a complication of Alzheimer's disease in Down syndrome.[19,20] A common mechanism underlying these conditions is amyloid deposition, with increased risk for amyloid angiopathy,[21,22] which might also be related to development of peripheral vascular disease. This finding is the first clear evidence for peripheral vascular disease association in Down syndrome, vascular factors and hypotension might be implicated, given that young individuals with Down syndrome have been shown to have reduced peripheral regulation of blood flow.[23] Further research into such mechanisms is required.

With regards to the cluster analysis, we confirmed that certain common morbidities in Down syndrome tend to cluster together, and that Down syndrome is associated with a unique combination of health conditions, including congenital heart disease, obstructive sleep apnoea, endocrine conditions, and Alzheimer's disease. Many of the conditions associated with Down syndrome appear to follow an accelerated ageing pattern. The mechanisms for this pattern remain unclear, but they might be caused by an overexpression of specific genes on chromosome 21, such as superoxide dismutase type 1 resulting in oxidative stress, which could differentially affect susceptible body systems.[24] However, our results highlight that not all conditions demonstrated the same accelerated ageing pattern. Despite the relative protection against cardiovascular risk factors such as hypertension and hypercholesterolaemia in Down syndrome, these nonetheless clustered together with cerebrovascular disease and ischaemic heart disease. Although cerebrovascular disease has been associated with amyloid deposition in Down syndrome, particularly cerebral amyloid angiopathy,[25] our results suggest that general cardiovascular risk factors could be relevant and thus a potential target for intervention to reduce Alzheimer's disease morbidity in Down syndrome.

In people with intellectual disabilities from other causes than Down syndrome, health conditions clustered in similar ways as in the general population with a few notable exceptions. These exceptions included congenital conditions, such as epilepsy and seizures and congenital heart disease, and an association between psychosis and obesity, potentially because of the high rates of antipsychotic prescription in individuals with intellectual disabilities.[26]

Our findings confirm that in Down syndrome, targeted surveillance and specialist knowledge of the features of conditions are required to minimise long-term risk, given their genetic predisposition. Important genetic risk factors include several genes triplicated in Down syndrome; for example, the *amyloid precursor protein (APP)*, associated with the development of Alzheimer's disease, the *autoimmune regulator (AIRE)*, and four of the six interferon subunits associated with immune dysregulation in Down syndrome.[27,28] Studies have found anatomical and architectural abnormalities in the thymus of individuals with Down syndrome and dysregulation of naive CD4 and CD8 T cells with demonstrable advanced immune ageing in individuals with Down syndrome.[29] Intervening early and treating conditions adequately might therefore reduce the risk of developing related conditions in people with Down syndrome. However, our results also confirm the need for general risk-reduction strategies, particularly for cardiovascular risks that should not be overlooked in favour of addressing syndrome-specific needs. There continues to be disparities in surveillance, diagnosis, and treatment of common health conditions in people with intellectual disabilities, including those with Down syndrome, with ongoing premature mortality and excess morbidity identified in these groups.[30]

The differences in incidence patterns across the lifespan between the groups have important clinical diagnostic and policy implications. For example, obstructive sleep apnoea in Down syndrome is often underdiagnosed despite a high reported incidence.[31] Its cause is linked to several conditions, including anatomical abnormalities (macroglossia, adenotonsillar hypertrophy, and midface hypoplasia), obesity, hypotonia, and hypothyroidism.[32] Similarly, Alzheimer's disease can be difficult to diagnose in people with Down syndrome, but new onset of seizures or stroke could be indicators of the disease. By recognising the relationship between different conditions in Down syndrome, more comprehensive assessment schedules can be implemented to improve diagnosis and management of these conditions, ultimately improving health outcomes for people with Down syndrome. To realise this, people with Down syndrome may require access to specialised expertise and support, as recognised in the new Down Syndrome Act in England,[33] the first country to implement a law on the care of these individuals, while in the USA a congressional directive called for a new trans-NIH research initiative known as the INCLUDE project. Furthermore, a more targeted approach to annual health screening in primary care might be required.

Our results provide support for guidelines for people with Down syndrome, which have so far lacked robust evidence.[34] Current guidelines recommend thyroid monitoring and obstructive sleep apnoea assessment,[4] but the guidance for conditions such as diabetes is less clear. Despite the observational nature of the evidence, we suggest guidance could be further improved by implementing age-specific health surveillance and prevention strategies, informed by knowledge of disease patterns over the lifespan (appendix p 14).

Prevention strategies could include appropriate exercise programmes for young people with Down syndrome to address the earlier onset of obesity and cognitive decline,[35] and regular assessment for conditions at the right time, such as for diabetes in young people with Down syndrome who have higher rates than their peers.[36] Priority should be given for vaccination,

particularly against respiratory pathogens given the immune dysfunction and increase in chronic respiratory disease.[18] The increased incidence of dental inflammation in both Down syndrome and intellectual disabilities individuals confirms this as an area of need for people with intellectual disabilities,[37] requiring regular dental check-ups alongside provision of reasonable adjustments.

To the best of our knowledge, this is the largest study of multiple morbidity in Down syndrome and those with other forms of intellectual disabilities to date in comparison with the general population. It provides a comprehensive description across the lifespan and highlights the unique health needs of people with Down syndrome. Our study has some limitations. People with Down syndrome were matched on sex, age, and family practice to controls; however, matching in the study design does not control for confounding by the matching factors, therefore we included age and sex in our analysis.[38] Future studies could evaluate sex differences in morbidity patterns given that sex might introduce effect modification. The large sample size allowed for a cluster analysis and suggested common mechanisms for morbidity clustering. The CPRD includes data collected in clinical practice and only data classified as being up to standard for research were analysed, but incomplete and misclassified records could bias estimates. We acknowledge that events recorded only in text entries could not be analysed and this shortcoming might have led to underestimation of rates. Following studies using electronic health records, we equated the not-recorded condition with the absent condition; we acknowledge that the proportion missing and the pattern of missingness could vary between conditions. Dates of events might be misclassified if recorded after discharge from hospital. However, arguably delays might be negligible in this study given that we reported incidence rates calculated with person-years. The geographical coverage of GPRD GOLD has changed over time, with lower representation in England in more recent years, owing to changes in the use of the Vision practice system. There are secular changes in the prevalence of common conditions, including asthma and diabetes, but it was beyond the scope of this research to evaluate possible period and cohort effects. Our Poisson models did not explicitly incorporate the general practice level but sensitivity analyses using robust variance estimates showed no difference in interpretation. General practice correlation for prevalence measures was appreciable, particularly for mental health outcomes, but it was not feasible to incorporate this in MCA models. Because of the nature of CPRD data, it might not include long-term data on all participants (eg, when family practices change software or when patients move between practices). These dropouts, and changes to diagnostic and coding practices, could have affected estimates over the study period. These limitations are mitigated by the large number of participants that contributed data. Certain conditions might be under-recorded in primary care (eg, obstructive sleep apnoea and mental health conditions), which could have affected IRRs. Although we included the most common conditions associated with Down syndrome, our list was not exhaustive. We made comparisons between Down syndrome and other patients with intellectual disabilities; however, we acknowledge that the intellectual disability comparator group was heterogeneous, and further investigation of subgroups of intellectual disabilities might be merited. Down syndrome is associated with early mortality, which might have affected morbidity estimates.[1] The clustering analysis was limited to people 75 years and younger because of the life expectancy of people with Down syndrome, which could have affected the grouping of ageing-related conditions in the general population. Moreover, clusters, and to a lesser extent conditions, represent broad groupings of diagnostic terms, and the frequency of specific diagnoses might vary across the patient groups studied. Finally, our aim was to take a lifespan perspective to examining the new onset of morbidities in people with Down syndrome; we did not focus on specific developmental periods, we did not include deprivation measures, nor did we examine chronicity of conditions. These aspects could be considered in future work.

In conclusion, these data contribute to our understanding of Down syndrome-specific risks of health conditions. The results suggest that adjustments to health-care guidance are required to improve care and outcomes of people with Down syndrome, to take into account the difference in age-related onset and syndromic clustering and provide clues for further examination of underlying mechanisms.

Contributors

RAB, SEP, LFC, AAA, MCG, and AS were involved in the conception, design, and conduct of the study. AS, MCG, and RAB planned the data analysis. RAB did the data analysis with help from MCG. All authors wrote, reviewed, and edited the manuscript. All authors had access to the data. RAB and MCG are the guarantors of this work, had full access to all the data in the study, and take responsibility for the integrity of the data and the accuracy of the data analysis.

Declaration of interests

We declare no competing interests.

Data sharing

Data were analysed under licence from the CPRD. Data sharing requests should be addressed to andre.strydom@kcl.ac.uk and might require further approval from the CPRD.

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