Morbidity and medication in a large population of individuals with Down syndrome compared to the general population

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AIM The aim of this study was to describe the incidence of morbidities and the prevalence of medical prescriptions in a large Down syndrome population.

METHOD A retrospective cohort study was carried out using the UK Clinical Practice Research Datalink from 1 January 2004 to 31 December 2013. We matched individuals with Down syndrome to randomly selected control participants by practice site, sex, birth year, and recording period.

RESULTS A total of 6430 individuals with Down syndrome (3009 females, 3421 males) and 19 176 controls (8966 females, 10 210 males) were included in the study. The incidence of cardiovascular disorders, gastrointestinal diseases (incidence rate ratio [IRR] 7.9 at 3 to <6y: yearly prevalence ratio [YPR] for laxatives 4.7), and sleeping disorders (IRR 4.8 in 3 to <6y) was increased in children with Down syndrome versus control participants. New onset of congenital heart malformation, ear diseases, eye disorders, autism, hypothyroidism, diabetes, and obesity were more frequent in childhood and remained elevated in adulthood (overall IRR 35.5, 1.7, 3.1, 4.4, 13.1, 1.3, and 2.6 respectively), whereas the gap widened in adulthood for epilepsy and intellectual disability (IRR 15.2 and 158 respectively, in participants older than 30y). At ≥10 years, the incidence of hypotension and dementia was raised (IRR 3.0 and 92.1 respectively; YPR for dementia drugs: 76.3); and that of hypertension, depression and anxiety was lowered (IRR 0.2, 0.5, and 0.4 respectively).

INTERPRETATION The profile of newly occurring morbidities in Down syndrome varies across the developmental lifespan.

The survival of individuals with Down syndrome has rapidly increased since the 1970s, from a median age at death below 10 years to mid-50s at present.1 Data on the occurrence of morbidities across the developmental lifespan are important for adequate management of people with Down syndrome, planning of healthcare resources, medical care guidelines, and implementation of screening strategies.1–3 However, the current evidence is mainly based on small-scale studies generally reporting prevalence rather than incidence (for which a large base population followed up over several years is needed),4–6 or focusing on hospital admissions or mortality rather than chronic morbidities.7–8 Past studies often did not include a comparator group, or compared rates with that of another population with intellectual disability rather than the general population.9,10

We therefore conducted an epidemiological study using a large primary care database. We estimated the age-specific incidence of preselected morbidities in individuals with Down syndrome with a focus on common cardiovascular, central nervous system, psychiatric, digestive, and endocrine disorders as previously reported in Down syndrome populations, and compared them to that in the general population. We similarly estimated the 1-year prevalence of selected prescriptions.

METHOD

Participants

Data source

Our matched retrospective cohort study used the United Kingdom Clinical Practice Research Datalink (CPRD). CPRD, which was started in 1987, is one of the largest anonymized databases of longitudinal primary care medical records worldwide.11 It is a resource routinely used in pharmaco-epidemiology and public health studies, and has led to 1350 articles being published in peer-review medical journals as of April 2015. The Medicines and Healthcare Products Regulatory Agency, part of the UK Department of Health, is the custodian of CPRD. General practitioners in the UK act as the gatekeepers to healthcare delivery via the National Health Service, which provides cover for the entire population. Data includes diagnoses, prescriptions,
laboratory tests, and referrals made by physicians. The integrity and completeness of the data are routinely assessed at patient and practice levels by CPRD custodians. Third parties request a license to access anonymized data. The recorded information is of high quality and over 350 diagnoses have been externally validated. The patients enrolled are also broadly representative of the UK population according to age, sex, and location. Our study received ethical approval from the Independent Scientific Advisory Committee of the CPRD (protocol number 13/166). As a condition of approval, outcomes affecting less than five Down syndrome patients may be shown in the figures but not in the tables in order to preserve anonymity.

**Individuals with Down syndrome**
Participants were all patients with at least one record for Down syndrome from the date of the patient’s registration until 31 December 2013 (Table S1, online supporting information). Females with a first record of Down syndrome after a pregnancy code were excluded. For each participant with Down syndrome, we randomly sampled up to three control participants within the same general practice and the same sex, birth year (±2y), and active period in the data (entry date ±2y and exit date ±2y) of the matched individual with Down syndrome.

**Follow-up**
Practices participating in CPRD are assigned an ‘up-to-standard’ date by CPRD custodians on reaching acceptable standards on ten practice-based measures of quality, completeness, and representativeness, marking suitability of longitudinal data records for general research purposes. The valid period for the analysis of morbidity and medication records started at the latest date of either 1 January 2004, the date at which the practice became up to standard, or the date of patient’s registration; and it finished at the earliest date of either 31 December 2013, the date of practice last collection, the date of patient’s registration; and the date of patient’s transfer out of database, or the date of death.

**Morbidity**
These were categorized according to the International Classification of Disease version 9 (ICD-9-CM). Read codes in CPRD were mapped to ICD-9-CM codes by two of the authors (MA, NF) and reviewed by a general practitioner with experience of CPRD data (HP). For obesity, records of diagnosis and body mass index records were used where available. Obesity in adults was defined as BMI ≥30kg/m². In individuals younger than 18 years old, age and sex-specific cut-offs were used (see Table SII, online supporting information). Morbidity categories were selected by the authors (OK and CW) based on literature and clinical experience. For presentation purposes, only morbidities with an incidence ≥1 per 100 person-years in individuals with Down syndrome are presented here, and morbidities with a lower incidence are available as Figures S1 to S4 (online supporting information).

**What this paper adds**
- Incidence of cardiovascular, gastrointestinal, and sleeping disorders was increased in children with Down syndrome versus control participants.
- Incidence of ear diseases and eye disorders, autism, epilepsy, intellectual disability, hypothyroidism, diabetes, and obesity was elevated in patients with Down syndrome at all ages.
- In adults with Down syndrome ≥30 years, the incidence of hypotension and dementia was raised; that of hypertension, depression, and anxiety was lowered.

**Medications**
Those prescribed were grouped according to the British National Formulary, except for drugs for the central nervous system which were subdivided into drugs for mental health and drugs for neurological disorders. A list of codes for medical prescriptions was created and reviewed by the authors to mirror as much as possible the list of morbidities.

**Statistical analysis**
The analysis was conducted on the whole study population and by age group. The incidence of morbidities was computed by dividing the number of first records of morbidity during the active period in the database by the total number of active person-years at risk for the Down syndrome and matched control groups separately. For incidence by age group, individuals with a record of morbidity before entry into the age group were excluded from the at-risk group. Due to the length of follow-up, some individuals belonged to several age groups over time and contributed to the computation of incidence in all of these age groups. Relative rate was calculated as the incidence rate ratio (IRR) for individuals with Down syndrome over matched controls. Prevalence of selected medications was calculated as a 1-year period prevalence for individuals with Down syndrome and matched controls for the period 1 January 2013 to 31 December 2013. For each group of medication, the yearly prevalence rate ratio (YPR) was calculated as the ratio of period prevalence of Down syndrome over controls. For additional analyses by age groups, all therapeutic records available between 1 January 2004 and 31 December 2013 were used.

The incidence rates, IRRs, and corresponding 95% confidence intervals (CIs) were computed using conditional Poisson regression, conditioning on each Down syndrome–control cluster. Data analysis was performed using SAS software version 9.2 (SAS Inc., Cary, NC, USA) and figures were drawn using STATA Statistical Software version 12 (StataCorp LP, College Station, TX, USA).

**RESULTS**
On 1 January 2013, there were 4 582 717 individuals enrolled in CPRD who belonged to 660 UK primary care practices. Using all records up to 31 December 2013, we identified 6430 individuals with Down syndrome (3009
females and 3421 males) followed up for a total of 29 920 person-years between 2004 and 2013. A subset of 2926 individuals with Down syndrome was present in the data on 1 January 2013 (1353 females and 1573 males); 891 (30.4%) under 18 years and 1449 (49.5%) under 30 years old. A total of 19 176 control participants (8966 females, 10 210 males) were selected with 89 739 person-years of follow-up, 8910 of which were active on 1 January 2013. A total of 6362 participants with Down syndrome had three matched controls (98.9%), and 68 had less than three (1.1%) matched controls: 33 had two matched controls (0.5%), 24 had one matched control (0.4%), and 11 did not have any (0.2%). Because of the matching, controls had the same age, sex, and follow-up distribution as individuals with Down syndrome (see Table SIII, online supporting information). The median duration of follow-up in Down syndrome individuals was 4.8 years (4.9y in controls) at 0 to under 3 years old, and was between 5.9 years and 8.4 years in older Down syndrome and controls groups.

Table I presents the incidence of new onsets of selected morbidities over the entire follow-up period in all individuals with Down syndrome and matched control participants (for more detail see Table SIV, online supporting information). Overall, the incidence of several disorders was significantly higher in participants with Down syndrome compared to the control population (p<0.001 except when specified): congenital heart disease (IRR 35.5; 95% CI 24.7–51.4), obstructive sleep apnoea (IRR 5.3; 3.8–248), autism (IRR 4.4; 3.1–6.4), intellectual disability (IRR 141.2; 86.9–229.3), hypothyroidism (IRR 13.1; 11.2–15.2), diseases of pulmonary circulation (IRR 6.3; 4.2–9.5), hypotension (IRR 2.9; 1.8–4.8), disorders of the ear (IRR 1.7; 1.6–1.9), disorders of the eye (IRR 3.1; CI 2.9–3.3), obesity (IRR 2.6; 2.4–2.8), gastrointestinal disorders (IRR 1.6; 1.4–1.7), diabetes (IRR 1.3; 1.1–1.6; p = 0.028), and dementia (IRR 82.7; 49.6–137.9). The incidence was significantly lower (p<0.001) for hypertension (IRR 0.32; 95% CI 0.27–0.39), anxiety (IRR 0.36; 0.28–0.44), depression (IRR 0.42; 0.37–0.49), and neurotic or personality disorders (IRR 0.54; 0.44–0.66).

The frequency of medical prescriptions to individuals with Down syndrome and matched controls mirrored incidence rates. Relative to controls, the YPRs for the most commonly prescribed drugs in 2013 were as follows (p<0.001 except when specified): dementia, 72.7 (95% CI 22.8–231.3); thyroid replacement therapy, 13.2 (11.3–15.5); psychoses and related disorders, 6.3 (4.8–8.2); laxatives, 5.5 (4.8–6.4); antiepileptic drugs, 3.9 (3.2–4.7); drugs used in parkinsonism and related disorders (p=0.008), 3.1 (1.6–5.9); insulins, 2.3 (1.6–3.4); and antacids, 3.3 (2.5–4.3) (Table SIV, online supporting information). In contrast, nitrates and calcium channel blockers drugs (YPR 0.4; 0.3–0.5), drugs for hypertension and heart failure (YPR 0.6; 0.5–0.7), and beta-adrenoceptor blocking drugs (YPR 0.1; 0.1–0.3) were less frequently prescribed (p<0.001).

There were important age-related variations in both morbidity incidence and medication prevalence. New onsets of ear and eye disorders were most frequent in childhood and remained elevated in participants 18 years and older. This was also apparent in the age-stratified prevalence of therapeutic prescriptions for these disorders (Fig. 1a,b). Congenital heart malformation had the highest incidence in infants younger than 3 years (IRR 117.2; 95% CI 28.0–236.9; p<0.001; and YPR for diuretics: 86.9;
New onset of gastrointestinal diseases was more common at all ages, and particularly elevated at ages 3 to under 6 years compared to controls (IRR 7.9; 3.9 – 15.8; \( p < 0.001 \); YPR for laxatives: 4.7; 3.8 – 5.81; \( p < 0.001 \)) (Fig. 2a). The incidence of hypothyroidism was elevated especially in children younger than 3 years (IRR 96.3; 23.5 – 394.7; \( p < 0.001 \)) (Fig. 2b). The relative incidence of obesity was high at all ages and peaked in children aged 3 to under 6 years with an incidence rate of 6.8 (95% CI 4.1 – 11.3; \( p < 0.001 \)) (Fig. 2c). Sleeping disorders were more frequent in childhood and mostly before age 12 years (IRR 4.8; 3.0 – 7.7; and 4.7; 3.2 – 7.1, in 3 to <6y and 6 to <12y respectively; \( p < 0.001 \)) (Fig. 3a). The incidence of epilepsy was elevated at all ages with a relative peak in adults 30 years and older (IRR 8.5; 7.3 – 9.8; \( p < 0.001 \)) (Fig. 3b). In children younger than 3 years, there was an excess incidence of infantile spasm (IRR 40.8; 5.3 – 312.9; \( p = 0.004 \)) that disappeared in older age groups. Incident diagnoses of intellectual disability were raised at all ages, and especially in adulthood (overall IRR: 141.2; 86.9 – 229.4) (Fig. 3b). Dementia developed at age group 30 years and older (IRR 92.1; 54.3 – 156.2; \( p < 0.001 \); YPR for dementia drugs: 76.3; 38.1 – 152.6; \( p < 0.001 \)) (Fig. 3d).

As for less common conditions with an incidence below 1 per 100 person-years, shapes of incidence rate by ages are represented in Figures S1 and S2. These show higher incidence rate in young children (<12y) for pulmonary disease (IRR 22.2; 6.6 – 74.9; \( p < 0.001 \) for <3y), obstructive sleep apnoea (IRR 17.6; 5.2 – 60.3; \( p < 0.001 \) for 3 to <6y), and hypertension (IRR 37.7; 4.9 – 290.7; \( p = 0.005 \) for <3y). A higher incidence rate was seen in young adults for diabetes (IRR 5.4; 2.7 – 11.0; \( p < 0.001 \) for 18 to <30y), and in older adults for hypotension (IRR 3.0; 1.7 – 5.5; \( p = 0.002 \) for \( \geq 30y \)). Diagnosis of intellectual disability had a high incidence at all ages, especially after 18 years of age (IRRs were >100 with significant \( p < 0.001 \)) (Fig. 3d). A lower incidence rate was observed for Down syndrome versus controls for depression and anxiety in adults from adolescence (IRR<0.5; \( p < 0.05 \) for \( \geq 12y \)), and for hypertension in adults 30 years and older (IRR 0.24; 0.19 – 0.29; \( p < 0.001 \)). Medication prevalence mirrored the shape of age-specific incidence of morbidities (Figs S3 and S4). A sensitivity analysis on Down syndrome cases matched to three controls.
DISCUSSION

We systematically described morbidities and medication use in individuals with Down syndrome and matched controls without Down syndrome using a large electronic medical record database. Our findings are discussed by type of morbidity.

**Cardiovascular disorders**

Congenital heart diseases were common in infants with Down syndrome, with an incidence rate of 18.8 per 100 person-years in the first 3 years of life, which matches reports in the literature of prevalence of up to 50%. This was also reflected in the high prevalence of prescription of diuretics: yearly prevalence in infants with Down syndrome aged ages 0 to under 3 years was 8.7%. However, our estimate of the incidence rate may be an underestimate as these congenital heart diseases are often managed by surgery performed in hospital and may not have been recorded by primary care physicians. Pulmonary diseases were rarer (incidence rate 1.3 per 100 person-years in <3y) but still markedly elevated in young children with Down syndrome (IRR 22.2 in this age group). A previous study shows that pulmonary hypertension may affect approximately 5% of infants with Down syndrome.

In adults with Down syndrome aged 30 years and older, compared to controls, hypertension was less likely to be diagnosed (IRR 0.24) and antihypertensive drugs were less likely to be prescribed (YPR 0.27), whereas hypotension was more frequently diagnosed (IRR 3.0). In absolute terms, the incidence rate of hypertension was 0.58 per 100 person-years, and that of hypotension was 0.15 per 100 person-years in adults with Down syndrome aged 30 years and older. There is an absence of prior large-scale epidemiological evidence for hypotension in Down syndrome population. Mechanisms are yet unknown, whereas several observations made in the Down syndrome population point to alterations in vascular regulation (e.g. increased expression of cystathionine β-synthase, an enzyme coded by a gene located on chromosome 21; or lack of catecholamine release in response to physical exercise).

**Diseases of CNS and sensory organs**

The incidence rate for sleeping disorders, and particularly obstructive sleep apnoea, in children was increased as...
Another common disorder in Down syndrome is epilepsy, which is thought to affect 8% of children with Down syndrome. Reviews suggest peaks of onset during infancy and another coincident with the emergence of Alzheimer’s disease in later adulthood. We confirmed a bimodal age at onset of epilepsy with high incidence rates, specifically infantile spasms in young children (IRR 40.8 in <3y for infantile spasm) and in adults aged 30 years and older (IRR 15.2).

Our study shows that the eye is the most common sense organ affected, with the incidence of an eye disorder as high as 28.1 per 100 person-years in under 3 years old. Guidelines encourage continuous monitoring of eye disorders in children with Down syndrome. Hearing loss also occurs soon after birth in infants with Down syndrome, and affects between one-third and two-thirds of all individuals with Down syndrome. Notably, the incidence rate decreased with age but remained relatively elevated in people with Down syndrome compared to controls at ages 3 years and older (peak in IRR of 2.9 at ages 12–18y).

In later life, dementia has been reported to begin 10 to 20 years earlier in the Down syndrome population previously observed. Another common disorder in Down syndrome is sleeping disorders and anxiolytic drugs, which is thought to affect 10% of children with Down syndrome. Reviews suggest peaks of onset during infancy and another coincident with the emergence of Alzheimer’s disease in later adulthood. We confirmed a bimodal age at onset of sleep disorders and anxiolytic drugs with high incidence rates, specifically infantile spams in young children (IRR 40.8 in <3y for infantile spasm) and in adults aged 30 years and older (IRR 15.2).

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Figure 3: Age-specific incidence rates per 100 person-years and prevalence of therapeutic prescription per 100 persons in 6430 individuals with Down syndrome and 19 176 matched controls (Clinical Practice Research Datalink, 2004–2013). Please note scales are different for Figures 1–3. Morbidities with an incidence rate <1 per 100 person-years with Down syndrome are represented in Figures S1 and S2.
compared to the general population and to be highly prevalent by middle age. In a study of individuals with Down syndrome aged 45 years and older, the prevalence of dementia doubled with each 5-year interval up to age 60 years. In an earlier study, the mean age at onset of dementia was 56 years old; the prevalence increased from 11% in the fourth decade to 77% in the sixth decade, and 100% in people with Down syndrome aged 70 years and older. In our study, the median age was 47 years in individuals with Down Syndrome of the age group ‘30 years and older’ on 1 January 2013, and the incidence of dementia at this age was more than 90 times higher in individuals with Down syndrome versus controls.

**Psychiatric and cognitive disorders**

The diagnosis of Down syndrome has been associated with psychiatric disorders throughout the lifespan. The IQ of children with Down syndrome has been shown to decrease during the first decade with a cognitive plateau reached in late childhood. This may partially explain the rapid increase in diagnosis of intellectual disability in individuals with Down syndrome 18 years of age and older in our study, with the incidence rate significantly rising from <0.5 per 100 person-years to over 3 per 100 person-years. However we note that the incidence rates were still low at any age, suggesting there may be under-recording by physicians of a diagnosis considered part of Down syndrome.

Over a quarter of adults with Down syndrome are thought to have a psychiatric disorder, most frequently major depressive disorders or behavioural disorders, and previous studies have shown the emergence of depression in adulthood. In our analysis the incidence of anxiety, depression, and neurotic disorders was lower in the Down syndrome population compared to control participants, with a gap starting during adolescence and widening in adulthood. The reason for this is unclear, but may include difficulty in establishing diagnosis in individuals with Down syndrome suffering from early onset dementia. Reported under-use of healthcare resources by Down syndrome adults may also affect the recording of psychiatric conditions. The prescription of hypnotics and anxiolytics in individuals with Down syndrome was increased compared to control participants, which raises safety issues associated with long-term use and dependence (overall YPR 2.6).

The incidence rate of behavioural disorders was low in our study and may reflect difficulties in assessing the diagnosis in children with Down syndrome. Recognition of the dual diagnosis of Down syndrome and autism has increased over the past decade. We observed a higher incidence of autism in children and adolescents with Down syndrome with IRR > 5 in individual aged 12 years and older. Autism is thought to affect around 6% to 7% of children with Down syndrome and the condition is often under-diagnosed in young children with intellectual disability, perhaps accounting for the low incident records in children with Down syndrome under 12 years in our study (incidence rate <1 per 100 person-years).

**Digestive system, endocrine and metabolic diseases**

Individuals with Down syndrome have reduced resting metabolic rates and the association of Down syndrome with obesity is well-established. In our study, the overall IRR was 2.6 and the incidence rate for obesity was already elevated in infants older than 3 years. This is concerning given the contribution of childhood obesity to other morbidities such as diabetes. The incidence of hypothyroidism was also elevated at any age in our study, confirming the importance of regular screening for thyroid disease from birth onwards. Individuals with Down syndrome were also likely to develop gastrointestinal diseases at all ages combined, and especially in early childhood.

**Strengths and weaknesses of the study**

Our results reinforce the need for close and routine monitoring of children and adults with Down syndrome for several morbidities. Our analysis is one of the largest to date to investigate the incidence of chronic morbidities in people with Down syndrome, making it suitable for the analysis of relatively rare morbidities of interest. In order to take into account recent changes in life expectancy in the Down syndrome population, we only analysed recent data collected over the last 10 years. To avoid underestimation of morbidities due to incomplete recording, the follow-up period included only periods when GP practice records were ‘up to standard’. Our analysis also included a large group of matched controls sampled from the CPRD database, a database representative of the general UK population. The median follow-up of individuals with Down syndrome was relatively long, therefore enabling reliable estimation of incidence rates.

While CPRD covers a very large population, we acknowledge several potential weaknesses. Delays may occur in making and recording diagnoses, the medical history may be incomplete, and diseases may only be apparent through prescriptions. Conditions that depend on patients accessing primary care services may have been less reliably recorded (e.g. sleeping disorders) compared to disorders for which the Down syndrome population is routinely screened (e.g. eye and ear disorders, gastrointestinal disorders). Among adults with Down syndrome living in the community, under-utilization of healthcare services and infrequent medical surveillance have been reported. Even when they seek help, some conditions may be specifically under-diagnosed in Down syndrome populations, such as psychiatric disorders. Given the known cluster of morbidities related to the primary Down syndrome diagnosis, general practitioners may be less inclined to record some conditions, such as intellectual disability, that are commonly associated with the primary diagnosis, or may be unable to confirm specific diagnoses (e.g. depression in an individual with Down syndrome with early onset dementia). Some of our Down syndrome cases were matched to less than three controls, creating an unbalanced design that may affect the results; however, this affected less than 2% of the Down syndrome cases and based upon the sensitivity analysis did not have a substantial impact. Finally, the apparent age differences in
IRR may in fact be due to younger individuals belonging to younger generations and vice versa. However, this bias is unlikely because of the design of our analysis, where individuals entered the data at any time during follow-up, and their follow-up was split into the different age groups they belonged to as they aged during the recording period.

CONCLUSION
We compared the incidence of selected morbidities in individuals with Down syndrome and matched controls using a large healthcare database with a long follow-up period. Individuals with Down syndrome have a substantial burden of medical, cognitive, and behavioural morbidities that evolve with age, which was reflected in higher prescription rates compared to the general population.

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SUPPORTING INFORMATION
The following additional material may be found online:

Figure S1: Age-specific incidence rates and prescription prevalence for selected morbidities and medications in individuals with Down syndrome and matched controls using CPRD data from 2004 to 2013.

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