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Rates, causes, place, and predictors of mortality in adults with intellectual disabilities with and without Down syndrome: cohort study with record linkage

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3 **Rates, causes, place, and predictors of mortality in**
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6 **adults with intellectual disabilities with and without**
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9 **Down syndrome: cohort study with record linkage**
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Abstract

Objectives

To investigate mortality in adults with intellectual disabilities: rates, causes, place, demographic and clinical predictors.

Design

Cohort study and record linkage to death data.

Setting

General community.

Participants

961/1,023 (94%) adults (16-83 years; mean=44.1 years; 54.6% male) with intellectual disabilities, clinically examined in 2001-2004; subsequently record-linked to their National Health Service number, allowing linkage to death certificate data, 2018.

Outcome measures

Standardised mortality ratios (SMRs), underlying, and all contributing causes of death, avoidable deaths, place, and demographic and clinical predictors of death.

Results

294/961 (30.6%) had died; 64/179 (35.8%) with Down syndrome, 230/783 (29.4%) without Down syndrome. SMR overall=2.24 (1.98, 2.49); Down syndrome adults=5.28 (3.98, 6.57), adults without Down syndrome=1.93 (1.68, 2.18); male=1.69 (1.42, 1.95), female=3.48 (2.90, 4.06). SMRs decreased as age increased. More severe intellectual disabilities increased SMR, but ability was not retained in the multivariate model. SMRs were higher for most ICD-10 chapters. For adults without Down syndrome, aspiration/reflux/choking, and respiratory infection were the commonest underlying causes of mortality; for Down syndrome adults "Down syndrome", and dementia were most common. Amenable deaths (29.8%) were double that in the general population (14%). 60.3% died in hospital. Mortality risk related to: percutaneous endoscopic gastrostomy/tube fed, Down syndrome, diabetes, lower respiratory tract infection at

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3 cohort-entry, smoking, epilepsy, hearing impairment, increasing number of prescribed
4 drugs, increasing age. Bowel incontinence reduced mortality risk.

7 **Conclusions**

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9 Adults with intellectual disabilities with and without Down syndrome have different SMRs
10 and causes of death which should be separately reported. They die younger, from
11 different causes than other people. Some mortality risks are similar to other people, with
12 earlier mortality reflecting more multi-morbidity; amenable deaths are also common.
13 This should inform actions to reduce early mortality, e.g. training to avoid
14 aspiration/choking, pain identification to address problems before they are advanced,
15 and reasonable adjustments to improve health-care quality.
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26 **Strengths and limitations of this study**

- 27 • Thorough methods of case ascertainment for intellectual disabilities at baseline.
- 28 • Individual verification of intellectual disabilities and its severity, and detailed health
29 assessments at baseline.
- 30 • Longitudinal design.
- 31 • Large cohort size and study duration, and successful record linkage for 94% of
32 participants.
- 33 • Limitations include that the study was conducted in only one part of Scotland, and
34 the reliance upon recorded cause of death from death certificates.
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Introduction

People with intellectual disabilities die at a younger age than other people; on average, 20 years younger,¹ or 28 years younger specifically for people with Down syndrome.² It has been demonstrated that people with intellectual disabilities receive poorer management of their long term conditions within primary health care services compared with the general population,³ and it is conceivable that this is one contributor to earlier mortality. It has been suggested that as many as 40% of deaths of people with intellectual disabilities may have been amenable to good quality health care.⁴⁻⁶

Previous studies on death in people with intellectual disabilities had limitations such as small sample sizes, or non-representative populations. More recently, there have been large-scale studies which are more representative, having been drawn from intellectual disabilities registers, or social security or primary care data with record linkage to death certification. These have been undertaken in parts of Sweden, Australia, England, Finland, Canada, Ireland, and USA (supplementary table 1).⁵⁻¹⁸ These studies fairly consistently report standardised mortality ratios (SMRs) to be high for people with intellectual disabilities, more so at younger ages, and higher for women than men. Adult studies have tended to report SMRs in the region of 2-4, although in some, SMR is only slightly above 1.^{10,18} However, direct comparison between studies is not always possible, due to the different age ranges studied and methods of reporting.

- Supplementary table 1 -

In view of the methods that studies have used for population identification (typically, routine administrative data linked to death certifications), they provide little information on the socio-clinical factors that influence SMR, or the risk factors associated with death, beyond that of age and sex. Three studies reported SMR by level of intellectual disabilities, with, broadly speaking, higher SMR with more severe intellectual

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3 disabilities.^{7,10,16} Only three studies (different studies to those that reported on level of
4 intellectual disabilities) were able to report data separately for adults with intellectual
5 disabilities with and without Down syndrome; two found higher mortality rates for adults
6 with Down syndrome (SMR=7.6,⁹ and hazard ratio=9.21⁵) than for adults without Down
7 syndrome, or an odds ratio showing Down syndrome as a risk of death.¹² A further
8 study reported SMR=5.5 for children and adults (combined) with Down syndrome, but
9 did not report SMR for those with intellectual disabilities without Down syndrome.¹⁹ Two
10 studies reported adults with intellectual disabilities to have higher SMRs if they have the
11 co-morbidities of epilepsy,^{5,7} and cerebral palsy,⁷ as opposed to not having these
12 comorbidities. One study reported adults with intellectual disabilities with comorbid
13 autism to have lower hazard ratios than those without comorbid autism.⁵ One study
14 reported the risk factors for mortality in a population with intellectual disabilities to be:
15 age, Down syndrome, cerebral palsy, blindness/low vision, technological
16 dependence/medical fragility, wheelchair dependence, mobility impairment without
17 wheelchair dependence, and epilepsy.¹² Factors not found to be risks, if any, were not
18 reported, and a further limitation was that factors were reported by agency staff, rather
19 than the individuals undergoing health assessments.¹² We have not identified any other
20 studies that investigated risk factors for time to mortality in adults with intellectual
21 disabilities.

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43 There is less consistency regarding the most common certified underlying causes of
44 death in adults with intellectual disabilities, partly as some studies do not report these
45 separately for children and adults, or by age ranges. Pneumonia, other respiratory
46 diseases, and diseases of the nervous system were reported to be the most common in
47 one study,¹¹ diseases of the circulatory system and respiratory systems in another,⁵
48 heart disease, neoplasm, and Alzheimer disease in a third,¹⁷ and diseases of the
49 circulatory system, neoplasm, and the nervous system in a fourth.¹⁸ In adults with
50 intellectual disabilities, cause specific SMRs have been reported to be high across most
51 groups of disorders.^{5,11} These studies did not report cause of death separately for adults

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3 with and without Down syndrome. Given the different health profile of people with Down
4 syndrome compared with people with intellectual disabilities of other causes, this is an
5 important limitation.²⁰ In people with Down syndrome, most studies on mortality have
6 been conducted with child populations. The most common causes of death in people with
7 Down syndrome have been reported to be congenital heart disease, and
8 pneumonia/diseases of the respiratory system.²
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17 Overall, the existing body of literature on mortality in adults with intellectual disabilities
18 does not include more detailed information on level of intellectual disabilities, nor
19 separate out the population with, from those without, Down syndrome (for whom causes
20 of death may differ), nor investigate health and demographic predictors of death other
21 than age and sex, and is inconsistent with regards to causes of death. A better
22 understanding of these factors may provide a pathway to action to reduce the observed
23 earlier mortality in adults with intellectual disabilities.
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33 This study aims to investigate the rates, causes, place, and demographic and clinical
34 associations with mortality in adults with intellectual disabilities, with and without Down
35 syndrome.
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41 **Methods**

42 ***Approval***

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46 Ethical approval was gained from NHS Greater Glasgow Primary Care Trust -
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48 Community & Mental Health Research Ethics Committee, and NHS Greater Glasgow and
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50 Clyde Safe Haven. Individual consent to participate was taken in line with Scottish law,
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52 between 2001-2004.
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Participants

The adult (aged 16+ years) intellectual disabilities population living within the NHS Greater Glasgow area was identified through multiple sources between 2000-2001. General practitioners were financially incentivised to identify their registered patients with intellectual disabilities, and all 631 (100%) did so. Adults were also identified via the intellectual disabilities health and social work services including day services, the Health Board register, and records of financial payments for any service by social work. This process led initially to an over-identification, such as people with IQ scores in the 70–80 range with additional complex health needs. All were systematically reviewed by nurses in the intellectual disabilities health service, and this group were removed. Thus, a register was compiled, and subsequently updated annually via general practices, with central support from the intellectual disabilities health service, until 2017 when services were redesigned. The identified adult prevalence of intellectual disabilities within the area was 3.33 per 1,000.

Process and data collection

With initial piloting in 2001, each participant had a detailed assessment of their general and mental health, and demographic factors, completed 2002-2004. One of six specially trained, registered nurses reviewed each person's primary health care records, then used a semi-structured tool, the C21st Health Check, to assess clinical factors and the level and cause of intellectual disabilities. In addition to a review of existing health problems and all bodily health systems, a physical examination was undertaken, including assessment of vision and hearing, measurement of height and weight, and a phlebotomy protocol followed. All information was then reviewed by the nurse with one of three general practitioners with a special interest in intellectual disabilities, and any further investigations that were indicated were completed. Previously known, and newly identified, conditions were then classified using the *International Statistical Classification of Diseases and Related Health Problems, 10th Revision (ICD-10)*.²¹ Anyone identified to have possible, probable, or definite mental ill-health, autism, or problem behaviours was

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3 then fully assessed by the project's intellectual disabilities psychiatrists. Each person's
4 assessment findings were then case conferenced by the two Consultant psychiatrists,
5 and diagnoses were derived and agreed according to clinical diagnoses, *ICD-10*
6 (*Diagnostic Criteria for Research*),²² *Diagnostic and Statistical Manual of Mental*
7 (*Disorders-IV-TR*),²³ and *Diagnostic Criteria for Psychiatric Disorders for use with Adults*
8 (*with Learning Disabilities (DC-LD)*).²⁴ Information was also collected on demographics,
9 and community, hospital, and social service use. Further details are provided
10 elsewhere.^{25,26} The data were entered into a database by two dedicated data-entry staff.

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12 Each person in Scotland is given a number unique to them at birth or first registration
13 with a general practitioner, which is used in almost all subsequent health service
14 encounters, and on certification of death. The numbers are held on the Community
15 Health Index (CHI) database at National Services Scotland. These CHI numbers provided
16 a means to record link each participant with National Records for Scotland death
17 certification data. This linkage was performed in 2018, and the linked data were held in
18 the NHS Greater Glasgow & Clyde (NHS GG&C) Safe Haven. Data on immediate,
19 underlying, and contributory causes of deaths by ICD-10 codes, age at death, and place
20 of death were extracted.

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22 In order to provide finer granularity of cause of death, and in view of the recognised
23 issue of variation between health staff in distinguishing and recording immediate, two
24 clinical academics then grouped individual causes of death into narrower groupings than
25 those provided by ICD-10 chapter headings (supplementary table 2).

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27 - Supplementary table 2 -
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30 **Analyses**

31 All statistical analyses were conducted using R for Windows v3.3.0 or SAS 9.3 (SAS
32 Institute, Cary NC) and were performed within the NHS GG&C Safe Haven environment.

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3 Due to disclosure principles of the Safe Haven, results with counts of less than 5 cannot
4 be released; these have been referred to as <5 throughout. Similarly, if it is deemed
5 possible that participants may be identified from the results, these may be omitted.
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7 Details are provided if this occurred.
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13 Data were summarised for the population of adults aged 16+ years with intellectual
14 disabilities. Categorical variables were summarised with the number and percentages of
15 people falling into each category and the number of missing data. Continuous variables
16 were summarised with the number of observations and those missing, the mean and
17 standard deviation (SD), and the minimum and maximum values, unless otherwise
18 stated.
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27 Participant characteristics were summarised overall and for those alive and those
28 deceased. For those who are deceased, their data including age at death,
29 underlying/contributing causes of death, and location of death were summarised for
30 those with and without Down syndrome. Location codes for place of death are provided
31 where available. We have assumed that those with the code for non-institutional location
32 to have died at home. Due to small numbers, location codes have been grouped together
33 for NHS hospitals, home, and other hospitals/care facilities including hospices.
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43 Mortality incidence rates have been calculated using the number of deaths in the cohort
44 divided by the number of person years alive within the study period multiplied by
45 100,000, overall and for those with and without Down syndrome. Standard mortality
46 ratios were calculated using population data for those aged 15 and over within NHS
47 GG&C in 2010.^{27,28} Death rates for males and females by 5 year band ages groups
48 spanning from 15-20 years old to 90 years and over were summed to form the expected
49 death rates for the general population. The observed death rate for adults with
50 intellectual disabilities was taken from our study results. The observed/expected death
51 rates were calculated for the intellectual disabilities cohort overall then separately by age
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3 group, sex, ability level, and for the adults with, and without, Down syndrome, and ICD-
4 10 chapter for cause of death, and compared to the general population.
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9 Deaths were also analysed for those that could be considered as deaths that would have
10 been avoidable. The Office for National Statistics (ONS) published a definition of
11 avoidable mortality,²⁹ which lists the causes of amenable deaths (deaths that should not
12 occur in the presence of good health care), and causes of preventable deaths, by ICD-10
13 codes. Causes of death for the adults with intellectual disabilities have been summarised
14 by ONS definition of avoidable deaths.
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23 To determine the demographic and clinical factors associated with death in adults with
24 intellectual disabilities, time to event analyses were explored using univariate Cox
25 Proportional Hazards models. Variables were selected as potentially relevant on the basis
26 of what is known on causes of death in people with intellectual disabilities, the 20 most
27 common physical health conditions reported in the adult population with intellectual
28 disabilities,²⁰ and other factors hypothesised as potentially clinically relevant
29 (supplementary table 3):
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- 37 • Demographics - 9 variables.
- 38 • Clinical conditions - 33 variables.
- 39 • Service use - 3 variables.
- 40 • Prescriptions - 5 variables.
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45 These models were then extended consider a single multivariable analysis and using a
46 stepwise regression method, a model of the factors most associated with death was
47 identified. Results from the univariate Cox Proportional Hazards models (Supplementary
48 table 3) and the multivariable model from the stepwise results have been presented with
49 hazard ratios with corresponding 95% confidence intervals (HR, 95% CI) and p-values
50 were obtained.
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60 - Supplementary table 3 -

Patient and public involvement

This study was designed to respond to the growing concern expressed by people with intellectual disabilities, their families, and third sector organisations about the early deaths of people with intellectual disabilities. The Scottish Learning Disabilities Observatory, where this research was undertaken, has a specific remit for people with intellectual disabilities. Its steering group includes partners from third sector organisations, including Down syndrome Scotland, and people with intellectual disabilities, who approved the work plan for this project prior to it commencing. Results from this study will be disseminated for people with intellectual disabilities in an easy-read version via the Scottish Learning Disabilities Observatory.

Results

Population characteristics

962 of the original 1,023 (94.0%) adults with intellectual disabilities were linked to a CHI number enabling the extraction of relevant death data. Reasons for the unlinked 61 people could be due to moving out of the area, or a recording mistake. 1 further participant was removed from the analysis due to inaccurate recording of dates, leaving 961 adults in the cohort (93.9%). Of these 961 adults, 294 (30.6%) had a record of death. Table 1 shows the baseline characteristics of the full cohort of 961, the adults who died, and those still alive at the time of linkage.

- Insert table 1 about here -

Age at death, and mortality incidence

The mean age at death was 61.0 years (SD=7.0 years). Of the 961 adults, 64 (35.8%) of the 179 adults with Down syndrome, and 230 (29.4%) of the 782 adults without Down syndrome had a record of death. Their mean age of death was 56.9 years (SD=4.3 years) for the adults with Down syndrome, and 62.2 years (SD=7.5 years) for

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3 the adults without Down syndrome. Mortality incidence for the cohort during the study
4 period was 3,049.0 per 100,000 person years follow-up, with 3,832.1 per 100,000 for
5 those with Down Syndrome and 2,885.0 for those without Down syndrome.
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10 11 **Standardised mortality ratios**

12 Compared with the general population, the SMR was 2.24 (1.98, 2.49) overall; 5.28
13 (3.98, 6.57) for adults with Down syndrome, 1.93 (1.68, 2.18) for adults without Down
14 syndrome; 1.69 (1.42, 1.95) for men and 3.48 (2.90, 4.06) for women. SMRs were
15 higher the more severe the level of intellectual disabilities, with people with profound
16 intellectual disabilities having an SMR of 4.14 (3.11, 5.17). SMR was high for all age
17 groups (though for the 15-25 year age group, the wide confidence interval includes one,
18 perhaps due to the smaller number of deaths in this group); this decreased as age
19 increased. SMRs were high for most ICD-10 chapter groups of conditions, particularly so
20 for congenital malformations at 17.26 (10.75, 23.78), diseases of the digestive system
21 at 16.13 (8.23, 24.04), mental and behavioural disorders at 12.64 (3.27, 22.00), and
22 external causes at 11.08 (3.40, 18.76). Details are shown in table 2.
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41 **Causes of death**

42 Cause of death data was available from death certificates for 262 (89.1%) of 294
43 participants who had died, which include 57 (89.1%) participants with Down syndrome,
44 and 205 (88.7%) participants without Down syndrome. Table 3 shows the underlying
45 causes of death by ICD-10 chapters separately for the adults with, and without Down
46 syndrome. For the whole cohort, diseases of the respiratory system were the most
47 common (21.8%), then diseases of the circulatory system (19.1%), then diseases of the
48 nervous system (13.0%), and neoplasms, followed by congenital anomalies (10.3%).
49 For the adults with Down syndrome, congenital anomalies were the most common (in all
50 cases this was a record of "Down syndrome"), then jointly diseases of the respiratory
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3 system and diseases of the circulatory system, then diseases of the nervous system,
4 followed by infections, and mental and behavioural disorders. For the adults without
5 Down syndrome, diseases of the respiratory system were the most common, then
6 diseases of the circulatory system, then neoplasms, then diseases of the nervous
7 system, followed by diseases of the digestive system. Table 4 presents the most
8 common underlying causes of death by individual causes, or related groups of causes,
9 with finer granularity than ICD-10 chapter headings (groups are shown in supplementary
10 table 2). Causes are listed in the order of how common they were in the whole cohort.
11 Data are presented separately for the adults with, and without Down syndrome. For the
12 whole cohort, the most common cause was aspiration/reflux/choking, then respiratory
13 infection, then other malignancy (non gastrointestinal), then other condition (mostly
14 unrelated conditions that could not be reported individually or as groups, due to
15 individually occurring at a frequency of <5). For the adults with Down syndrome, Down
16 syndrome was the most common cause, then dementia, then other infection. For the
17 adults without Down syndrome, aspiration/reflux/choking was the most common cause,
18 then respiratory infection, then other malignancy (non gastrointestinal).

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38 - Insert tables 3 and 4 about here -
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41 Table 5 shows the all contributing causes of death data, again presenting the most
42 common causes by individual causes, or related groups of causes with finer granularity
43 than ICD-10 chapter headings. Data is presented separately for the adults with, and
44 without Down syndrome. For the whole cohort, respiratory infection was the most
45 common cause (27.1%), followed by aspiration/reflux/choking (19.8%), other conditions
46 (15.6%), other cardiovascular conditions (non acute myocardial nor other ischaemic
47 heart disease: 14.5%), then other respiratory conditions. For the adults with Down
48 syndrome, Down syndrome was the most common, then dementia, then respiratory
49 infection, then aspiration/reflux/choking. For the adults without Down syndrome,
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3 respiratory infection was the most common cause, then aspiration/reflux/choking, then
4 other condition, then other respiratory conditions and intellectual disabilities.
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11 12 13 **Avoidable deaths**

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15 According to the ONS list of avoidable deaths, 102 (38.9%) of the 262 deaths were
16 avoidable; 78 (29.8%) were deaths that are amenable to good health care, whilst 51
17 (19.5%) were preventable deaths. 27 (10.3%) deaths were classed as both amenable
18 and preventable deaths. This compares to published Scottish death data showing in 2018
19 that 28% of deaths were avoidable; 14% amenable and 24% preventable, similar to the
20 figures in the previous four years (data not available prior to 2014).³⁰ For the 57 deaths
21 of adults with Down syndrome, 17 (29.8%) deaths were avoidable, 15 (26.3%) deaths
22 were amenable to good health care, whilst 7 (12.3%) were preventable. 5 (8.8%) were
23 both amenable and preventable. For the 205 deaths of adults without Down syndrome,
24 85 (41.5%) were avoidable, 63 (30.7%) deaths were amenable to good health care,
25 whilst 44 (21.5%) were preventable. 22 (10.7%) were both amenable and preventable.
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40 **Place of death**

41 Of the 262 participants for whom place of death was known, 158 (60.3%) died in an
42 NHS Hospital, 70 (26.7%) died at home, and 34 (13.0%) died within other
43 hospitals/care facilities. This was similar for both the adults with Down syndrome: 31
44 (54.4%) in an NHS hospital, 17 (29.8%) at home, and 9 (15.8%) within other
45 hospitals/care facilities; and the adults without Down syndrome: 127 (62.0%) in an NHS
46 hospital, 53 (25.9%) at home, and 25 (12.2%) within other hospitals/care facilities.
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Factors associated with risk of death

The results from the univariate cox proportional hazards models indicated that of the original 50 potential variables, factors associated with risk of death were (supplementary table 3):

- Demographics – age, more severe learning disabilities, accommodation type (not living with family carer), not having day-time occupation, and being a smoker (but not sex, the extent of neighbourhood deprivation, civil status, nor Down syndrome, in view of the confidence intervals).
- Clinical conditions – having spastic quadriplegia, hearing impairment, visual impairment, diabetes, percutaneous endoscopic gastrostomy/tube fed, constipation, ataxia/gait disorder, osteoporosis, hypertension, dysphagia, dyspnoea, gastro-oesophageal reflux disorder, lower respiratory tract infection, total number of physical health disorders, not having impaired mobility, not having urinary incontinence, not having bowel incontinence, and not having autism (but not epilepsy, body mass index, nail disorder, epidermal thickening, cerebral palsy, fungal infection, musculoskeletal pain, bone deformity, dental/oral problem, eczema/dermatitis, psychosis, affective disorder including bipolar affective disorder, problem behaviour, eating disorder including pica, nor any mental illness).
- Service use – number of general practitioner consultations in the previous 12 months, total number of different types of health professionals providing care at the time of the clinical assessment, (but not number of accident and emergency attendances in the previous 12 months).
- Prescriptions – antiepileptic drugs, total number of different types of drugs, (but not antipsychotic drugs, antidepressant drugs, nor anxiolytic drugs).

Table 6 shows the final model of the variables retained in the multivariable analysis for time to death. The significant factors indicating an increased risk of death were increased age, smoking, Down syndrome, diabetes, being percutaneous endoscopic gastrostomy/tube fed, lower respiratory tract infection at cohort inception, epilepsy,

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3 hearing impairment, and total number of different types of drugs prescribed, whilst
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5 bowel incontinence showed a reduced risk of death. Of note, level of intellectual
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7 disabilities whilst significant in the univariate analysis, was not retained in the
8
9 multivariable model.

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13 - Insert table 6 about here -
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17 **Discussion**

18 ***Principle findings and interpretation***

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22 As far as we are aware, this is the first population-based study of adults with intellectual
23
24 disabilities to report in detail the factors associated with time to death, and to describe
25
26 their causes of death and quantify the SMR separately for adults with Down syndrome
27
28 and adults without Down syndrome. This is important, since adults with Down syndrome
29
30 form a notable proportion of all adults with intellectual disabilities (19% in this cohort),
31
32 and because they have a different pattern of clinical conditions compared with other
33
34 adults with intellectual disabilities.²⁰ We found that aspiration/reflux/choking is the most
35
36 common underlying cause of death in adults with intellectual disabilities, followed by
37
38 respiratory infection. They are also the most common all contributing causes of death.
39
40 The profile differed in the adults with Down syndrome for whom "Down syndrome",
41
42 followed by dementia, were recorded as the most common underlying cause of death,
43
44 and all contributing causes of death; with the next most common all contributing cause
45
46 of death being respiratory infection, then aspiration/reflux/choking. The proportion of
47
48 deaths that would have been amenable to good care for adults with intellectual
49
50 disabilities was more than double that seen in the general population. Although
51
52 aspiration/reflux/choking is not included in the ONS list of avoidable deaths, and
53
54 therefore not included in the figures we report on amenable deaths, we consider that
55
56 good care could have prevented many of these deaths. This appears to be very
57
58 important for adults with intellectual disabilities irrespective of whether they have Down
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3 syndrome. Similarly, some other causes of deaths within this cohort, such as
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5 constipation/mega-colon, and urinary tract infections do not appear on the ONS list of
6
7 avoidable deaths.
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11 Clearly, this pattern of causes of death differs from that seen in the general population,
12
13 in whom the most common underlying causes of death are heart disease, then dementia,
14
15 then lung cancer in men, and dementia, then heart disease, then stroke in women.³¹
16
17 When all cancers are grouped together, in the general population, cancer is the leading
18
19 underlying cause of death in 30% of men and 26% of women, compared with this study
20
21 reporting 0% for adults with Down syndrome, and 15.2% for adults with intellectual
22
23 disabilities without Down syndrome – presumably as the adults with intellectual
24
25 disabilities are dying younger from other causes, and cancers increase with age.
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29 We found an overall SMR of 2.24; 5.28 in the adults with Down syndrome and 1.93 for
30
31 the adults without Down syndrome. SMRs were higher for most ICD-10 chapter
32
33 groupings of conditions. It was higher in the women than the men, as has been
34
35 previously reported in most (supplementary table 1), but not all^{10,18} previous reports.
36
37 The reason for this is unknown; in the general population, mortality rates have fallen in
38
39 recent decades, and more so in middle and older aged men than women (i.e. the sex
40
41 gap is narrowing at these ages), but we do not know what trends over time there have
42
43 been for people with intellectual disabilities. Having intellectual disabilities removes
44
45 differences in lifespan by sex compared with the general population; but sex was not a
46
47 predictor of mortality in our study, so the SMR difference may only be because of the
48
49 difference found in the general population by sex. SMRs were lowest with older age
50
51 groups, likely to be due to increased illness in the older general population and
52
53 conversely a healthier group with intellectual disabilities living to older ages compared
54
55 with those who die younger. Although SMR was higher with increasing severity of
56
57 intellectual disabilities, ability level was not retained within the multivariable model on
58
59 time to death. The factors that were independently associated with increased risk of
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3 death, in order, were being percutaneous endoscopic gastrostomy/tube fed, Down
4 syndrome, diabetes, having a lower respiratory tract infection at entry to the cohort,
5 smoking, epilepsy, hearing impairment, total number of prescribed drugs, and age,
6 whilst bowel incontinence had a reduced risk of death. Some of these predictors are
7 similar to those reported in the general population, suggesting earlier mortality of adults
8 with intellectual disabilities is largely accounted for by the higher rates of multi-
9 morbidities that they experience compared with other people, and amenable deaths.³²
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11

12
13 Whilst accommodation type (not living with a family carer), ability level, not having day-
14 time occupation, having spastic quadriplegia, visual impairment, constipation, ataxia/gait
15 disorder, osteoporosis, hypertension, dysphagia, dyspnoea, gastro-oesophageal reflux
16 disorder, total number of physical health disorders, not having impaired mobility, not
17 having urinary incontinence, and not having autism, number of general practitioner
18 consultations in the previous 12 months, total number of different types of health
19 professionals providing care at the time of the health assessment, and antiepileptic
20 drugs were related to time of death on univariate analyses, they were not retained in the
21 multivariable model.
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40 The majority of the adults with intellectual disabilities, with and without Down syndrome,
41 died in an NHS hospital.
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45 ***Comparison with previous literature***

46
47 The overall SMR we report, higher SMR in women than men, and higher SMR at younger
48 age groups is similar to the majority of previous reports. Most mortality studies with
49 people with Down syndrome have been conducted with children. Previous reports of
50 children and adults (combined) gave an SMR=5.5,¹⁹ and for adults SMR=7.6,⁹ compared
51 with our finding for adults with Down syndrome of SMR=5.28. Recent systematic reviews
52 reported people with intellectual disabilities on average died 20 years younger than other
53 people, and people with Down syndrome died 28 years younger, although the majority
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3 of the Down syndrome studies were not recent.^{1,2} In our study we found the gap
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5 between the age at death of people with intellectual disabilities with and without Down
6
7 syndrome to be only 5.3 years, possibly reflecting the increasing lifespan of people with
8
9 Down syndrome exceeding increases in lifespan for people with intellectual disabilities
10
11 without Down syndrome. Notably, after "Down syndrome", dementia was the most
12
13 commonly reported underlying, and all contributing cause of death for the adults with
14
15 Down syndrome, whereas studies in the past commented on congenital heart disease
16
17 and respiratory causes.
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21 For the cohort overall, respiratory infection and aspiration/reflux/choking were the most
22
23 common all contributing causes of death. These conditions feature in previous studies on
24
25 causes of death^{5,6,8,10,11}, although there are inconsistencies between studies. By ICD-10
26
27 chapter, our study found the most common underlying causes of death were diseases of
28
29 the respiratory system, then of the circulatory system, followed by neoplasms. Others
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31 reported the most common to be vascular,¹⁰ circulatory,⁵ heart disease,¹⁷ and jointly
32
33 circulatory and neoplasm.¹⁸
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36
37 Studies that investigated avoidable deaths in adults with intellectual disabilities found
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39 them to be more common than in the general population, due to deaths that would have
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41 been amenable to good care. Avoidable deaths have been reported in 44.7% of deaths
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43 of people with intellectual disabilities in England (mostly amenable deaths – figure not
44
45 reported),⁶ and in 31% in Australia,¹⁸ compared with our figure of 38.9%. Avoidable
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47 deaths that would have been amenable to good care have been reported to occur in 37%
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49 of deaths of people with intellectual disabilities in England.⁵ Our figure is slightly lower at
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51 29.8% but still more than double that found in the Scottish general population.³⁰ It
52
53 should be noted that the ONS list of avoidable deaths was not designed specifically for
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55 people with intellectual disabilities, and it may emphasise some causes less relevant, and
56
57 omit others that might be highly relevant in this population.⁵
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Strengths and limitations

The strengths of the study include the thorough methods of case ascertainment for intellectual disabilities at baseline with verification of intellectual disabilities and its severity, suggesting results are generalisable in other high income countries. Additionally, there were detailed clinical assessments at baseline, and a longitudinal design. The size of the cohort and the duration of follow-up is also a strength, as is the successful record linkage for 94% of participants. Our study does have a couple of limitations, specifically that the study was only conducted in one region of Scotland, and the reliance upon death certificate data to obtain cause of death.

Implications

It is important to know the factors that are associated with risk of death, and the common causes of death in this population, as these then inform the actions needed to reduce the unacceptably high SMRs experienced by people with intellectual disabilities. It is not adequate to solely rely on the public health interventions available to everyone, even when they are accessible. Aspiration, reflux, and choking could, and should, be avoided by raising awareness of its consequences (death), and putting in place training on simple measures related to feeding, positioning, food consistency, and when to seek health advice from speech and language therapy, physiotherapy, nursing, and medical advice. Carers need to be aware of how the adults they care for express pain, so that conditions such as gastrointestinal ulcers are attended to, prior to the extreme point of perforation, and so treatable conditions such as constipation and urinary tract infections are managed before they lead to respiratory distress and sepsis. Quality of care is important; adults with intellectual disabilities need just as good care for their diabetes and epilepsy (and other conditions) as the rest of the population, with reasonable adjustments to address accessibility, and accessible smoking cessation programs.

Future research

Further research on larger samples is needed, particularly with regards to replicating and extending our findings on the factors that are associated with risk of death, and any sex differences in them, so that practitioners can focus on actions to improve the life expectancy of adults with intellectual disabilities, with and without Down syndrome.

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53 analysis, and interpretation of data; in the writing of the report; and in the decision to
54 submit the article for publication.
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60 The researchers are independent from the funders.

Competing interests

The authors declare no competing interests.

Author's contributions

S-AC is principle investigator, she conceived and managed the project, interpreted data, and wrote the first draft of the manuscript. LA contributed to the conception of the project, and project management. NG designed and supervised the statistical analysis, and contributed to data interpretation and drafting of the manuscript. PMcS implemented and refined the statistical analysis, and contributed to data interpretation, and drafting of the manuscript. AJ implemented and refined the statistical analysis, and contributed to data interpretation. AH contributed to data linkage and interpretation, and drafting of the manuscript. CMcC provided expertise on data linkage and methods, and drafting of the manuscript. DK contributed to data interpretation and drafting of the manuscript. CM contributed to data interpretation, and drafting of the manuscript. All approved the final version of the manuscript. S-AC is the study guarantor.

Data sharing

Data is available via NHS GG&C safe haven upon application.

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Table 1. Cohort characteristics at time of the health assessment, summarised overall and by death status during the follow-up period

Variable	Statistics / Groups	All participants (N=961)	Deceased participants (N=294)	Alive participants (N=667)
Age (years)	Mean (SD)	44.1 (14.6)	52.4 (13.6)	40.5 (13.6)
	Min, max	16, 83	18, 83	16, 77
Age group	16-25 years	127 (13.2%)	10 (3.4%)	117 (17.5%)
	26-35 years	153 (15.9%)	26 (8.8%)	127 (19.0%)
	36-45 years	246 (25.6%)	49 (16.7%)	197 (29.5)
	46-55 years	205 (21.3%)	85 (28.8%)	120 (18.0%)
	>55 years	230 (23.9%)	124 (42.0%)	106 (15.9%)
Sex	Male	525 (54.6%)	154 (52.4%)	371 (55.6%)
	Female	436 (45.3%)	140 (47.5%)	296 (44.4%)
Ability level	Mild ID	382 (39.7%)	92 (31.2%)	290 (43.5%)
	Moderate ID	236 (24.5%)	73 (24.7%)	163 (24.4%)
	Severe ID	180 (18.7%)	67 (22.7%)	113 (16.9%)
	Profound ID	163 (17.0%)	62 (21.1%)	101 (15.1%)
Accommodation type	Family carer	374 (38.9%)	70 (23.8%)	304 (45.6%)
	Independent	93 (9.7%)	36 (12.2%)	57 (8.5%)
	Paid support	435 (45.2%)	161 (54.6%)	274 (41.1%)
	Congregate care	59 (6.1%)	27 (9.2%)	32 (4.8%)
Down syndrome	No	782 (81.4%)	230 (78.2%)	552 (82.8%)
	Yes	179 (18.6%)	64 (21.7%)	115 (17.2%)

ID=intellectual disabilities; SD=standard deviation

Table 2. Standardised mortality ratios

Variable	Groups	SMR (95% CI)
All participants	-	2.24 (1.99, 2.50)
Age group*	15-25 years	18.73 (0.37, 37.09)
	26-35 years	4.21 (1.29, 7.13)
	36-45 years	3.86 (2.28, 5.44)
	46-55 years	3.77 (2.90, 4.74)
	>55 years	1.86 (1.60, 2.12)
Sex	Male	1.69 (1.42, 1.95)
	Female	3.48 (2.90, 4.06)
Ability level	Mild ID	1.60 (1.27, 1.92)
	Moderate ID	2.10 (1.62, 2.58)
	Severe ID	2.78 (2.11, 3.44)
	Profound ID	4.14 (3.11, 5.17)
Down syndrome	No	1.93 (1.68, 2.18)
	Yes	5.28 (3.98, 6.57)
Underlying causes of death grouped by ICD-10 chapter**	Congenital malformations, deformations and chromosomal abnormalities	17.26 (10.75, 23.78)
	Diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism	7.50 (-7.20, 22.20)
	Diseases of the circulatory system	5.55 (4.01, 7.09)
	Diseases of the digestive system	16.13 (8.23, 24.04)
	Diseases of the genitourinary system	3.65 (0.73, 6.57)
	Diseases of the musculoskeletal system and connective tissue	5.40 (-0.71, 11.52)
	Diseases of the nervous system	7.73 (5.13, 10.32)
	Diseases of the respiratory system	6.78 (5.02, 8.54)

	Diseases of the skin and subcutaneous tissue	2.75 (-2.64, 8.15)
	Endocrine, nutritional and metabolic diseases	3.43 (1.05, 5.81)
	External causes of morbidity and mobility	11.08 (3.40, 18.76)
	Infectious and parasitic diseases	8.93 (1.78, 16.07)
	Mental and behavioural disorders	12.64 (3.27, 22.00)
	Neoplasms	6.31 (4.19, 8.43)
	Symptoms, signs and abnormal clinical and laboratory findings, not elsewhere classified	19.51 (0.39, 38.63)

CI=confidence intervals; ID=intellectual disabilities; SMR=standardised mortality ratios

*Data used for comparison with General Population (GG&C Health Board) provides data in 5 year age bands therefore 15+. Data on adults with ID are 16+

** Negative Lower CI and wide CIs indicate low number of observed deaths in study population

Table 3. Underlying causes of death grouped by ICD-10 chapter, where cause of death is known

ICD-10 chapter	Participants with Down syndrome (N=57)	Participants without Down syndrome (N=205)
Certain infectious and parasitic diseases	5 (8.8%)	<5
Neoplasms	<5	33 (16.1%)
Diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism	0	<5
Endocrine, nutritional and metabolic diseases	0	8 (3.9%)
Mental and behavioural disorders	5 (8.8%)	<5
Diseases of the nervous system	7 (12.3%)	27 (13.2%)
Diseases of the eye and adnexa	0	0
Diseases of the ear and mastoid process	0	0
Diseases of the circulatory system	8 (14.0%)	42 (20.5%)
Diseases of the respiratory system	8 (14.0%)	49 (23.9%)
Diseases of the digestive system	0	16 (7.8%)
Diseases of the skin and subcutaneous tissue	0	<5
Diseases of the musculoskeletal system and connective tissue	0	<5
Diseases of the genitourinary system	<5	5 (2.4%)
Pregnancy, childbirth and the puerperium	0	0
Certain conditions originating in the perinatal period	0	0
Congenital malformations, deformations and chromosomal abnormalities	21 (36.8%)	6 (2.9%)
Symptoms, signs and abnormal clinical and laboratory findings, not elsewhere classified	0	<5
External causes of morbidity and mortality	<5	7 (3.4%)
All deaths	57 (100%)	205 (100%)

ICD-10=International Statistical Classification of Diseases and Related Health Problems, 10th Revision

Table 4. Underlying causes of death grouped by specific individual causes or related groups of causes, where cause of death is known

Causes	Participants with Down syndrome (N=57)	Participants without Down syndrome (N=205)
Aspiration/reflux/choking	<5	22 (10.8%)
Respiratory infection	<5	21 (10.3%)
Down syndrome	21 (36.8%)	0
Other malignancy	0	19 (9.3%)
Other condition	<5	17 (8.3%)
Epilepsies	<5	13 (6.4%)
Acute myocardial infarction	<5	13 (6.4%)
Gastro-intestinal malignancy	<5	12 (5.9%)
Stroke	<5	11 (5.4%)
Other cardiovascular disease	<5	11 (5.4%)
Other respiratory condition	<5	9 (4.4%)
Other infection	5 (8.8%)	6 (2.9%)
Cerebral palsy	0	11 (5.4%)
Dementia	9 (15.8%)	0
Other gastrointestinal disorders	0	8 (3.9%)
Ulcer/gastrointestinal perforation	0	7 (3.4%)
Diabetes	0	7 (3.4%)
Other congenital condition	0	6 (2.9%)
Other ischaemic heart condition	0	6 (2.9)
Mental health	0	<5
Other neurological conditions	<5	<5
Renal failure	<5	<5
All deaths	57 (100%)	205 (100%)

Table 5. All contributing causes of death grouped by specific individual causes or related groups of causes, where cause of death is known

Causes	Participants with Down syndrome (N=57)	Participants without Down syndrome (N=205)
Respiratory infection	22 (38.6%)	49 (23.9%)
Aspiration/reflux/choking	11 (19.3%)	41 (20.0%)
Down syndrome	43 (75.4%)	<5
Other condition	8 (14.0%)	33 (16.1%)
Other cardiovascular disease	8 (14.0%)	30 (14.6%)
Other respiratory conditions	<5	31 (15.1%)
Other infection	9 (15.8%)	24 (11.7%)
Intellectual disabilities	<5	31 (15.1%)
Epilepsies	8 (14.0%)	24 (11.7%)
Dementia	24 (42.1%)	<5
Other neoplasms	<5	23 (11.2%)
Cerebral palsy	<5	24 (11.7%)
Acute myocardial infarction	5 (8.8%)	19 (9.3%)
Other gastrointestinal disorders	<5	18 (8.8%)
Diabetes	<5	19 (9.3%)
Other ischaemic heart disease	<5	19 (9.3%)
Renal failure	<5	16 (7.8%)
Stroke	<5	17 (8.3%)
Other congenital condition	<5	15 (7.3%)
Gastrointestinal malignant neoplasm	<5	12 (5.9%)
Ulcer/gastrointestinal perforation	<5	10 (4.9%)
Mental health	<5	10 (4.9%)
Other neurological condition	<5	8 (3.9%)
Heart failure	<5	7 (3.4%)
Injuries and accidents	<5	8 (3.9%)
Medical/surgical complications	<5	<5
Secondary malignancies	<5	<5
Thyroid disorders	<5	<5
Metabolic disorder	<5	<5
All deaths	57 (100%)	205 (100%)

Table 6. Multivariable model results for the outcome time to death

Variable		Hazard ratio	95% CI	p-value
Age		1.056	1.046, 1.066	<0.0001
Smoker	No	1	-	
	Yes	1.531	1.1011, 2.128	0.0112
Down syndrome	No	1	-	
	Yes	2.440	1.787, 3.332	<0.0001
Epilepsy	No	1	-	
	Yes	1.511	1.173, 1.946	0.0014
Hearing impairment	No	1	-	
	Yes	1.320	1.030, 1.692	0.0284
Bowel incontinence	No	1	-	
	Yes	0.490	0.376, 0.640	<0.0001
Diabetes	No	1	-	
	Yes	2.346	1.553, 3.542	<0.0001
PEG/tube fed	No	1	-	
	Yes	2.346	1.135, 5.989	0.00240
Lower respiratory track infection	No	1	-	
	Yes	1.782	1.315, 2.415	0.0002
Total number of prescribed drugs		1.066	1.016, 1.118	0.0085

CI=confidence interval; PEG=percutaneous endoscopic gastrostomy

Rates, causes, place, and predictors of mortality in adults with intellectual disabilities with and without Down syndrome: cohort study with record linkage

Supplementary table 1. Previously reported standardised mortality ratios, causes, and risks for death

Author	Country	SMR (95% confidence interval)	Number of deaths	Causes of death and risk factors for death
Forsgren et al (1996) ⁷	Sweden	4.2 (3.3, 5.3) at 20-59y; 1.1 (0.9, 1.5) at 60+y <i>Without epilepsy:</i> 3.8 (2.8, 5.0) at 20-59y; 1.1 (0.8, 1.5) at 60+y <i>With epilepsy:</i> 5.0 (2.9, 8.7) at 20-59y; 2.4 (0.9, 6.1) at 60+y <i>With epilepsy and cerebral palsy:</i> 8.0 (4.1, 15.7) at 20-59y; 0.9 (0.1, 6.6) at 60+y <i>M:</i> 1.6 (1.2, 2.0) at 0-60+y <i>F:</i> 2.6 (2.0, 3.3) at 0-60+y <i>Mild ID:</i> 1.8 (1.1, 2.7) at 0-60+y <i>Moderate ID:</i> 1.5 (1.1, 2.0) at 0-60+y <i>Severe ID:</i> 2.0 (1.5, 2.6) at 0-60+y <i>Profound ID:</i> 8.1 (5.6, 11.7) at 0-60+y	124 at 0-60+y; 112 at 20-60+y	<i>Underlying cause at 0-60+y:</i> Congenital anomalies: SMR=46.3 (32.9, 65.0) Nervous system: SMR=9.7 (5.5, 17.0) Mental disorder: SMR=4.0 (1.9, 8.4) Respiratory: SMR=3.3 (2.0, 5.5) Circulatory: SMR=2.1 (1.6, 2.7) Violent death: SMR=1.4 (0.6, 2.8) Neoplasm: SMR=0.9 (0.6, 1.6)
Durvasula & Beange (2002) ⁸	Australia	4.9 (3.4, 6.4) at 10-59y <i>M:</i> 4.1 (2.4, 5.9) at 10-59y <i>F:</i> 6.2 (3.3, 9.1) at 10-59y	40 at 10-59y; 31 at 20-59y	<i>Underlying cause at 10-59y:</i> Respiratory: 35% (pneumonia, aspiration) External causes: 20% Neoplasm: 17.5% Heart disease: 15% (congenital heart disease 50%) Gastrointestinal: 7.5% (ischaemic bowel, perforated peptic ulcer, post-operative peritonitis) Seizure: 5%
Tyrer et al (2007) ⁹	England	3.24 (2.93, 3.56) at 20-70+y <i>M:</i> 2.86 (2.50, 3.26) at 20-70+y <i>F:</i> 3.63 (3.12, 4.20) at 20-70+y 1.51 (1.23, 1.83) to 11.50 (8.14, 15.78) at 20-70+y <i>M:</i> 1.39 (1.03, 1.82) to 8.83 (5.60, 13.25) at 20-70+y <i>F:</i> 1.60 (1.18, 2.12) to 17.22 (9.64, 28.4) at 20-70+y <i>With Down syndrome:</i> 7.60 at 20-70+y <i>Without Down syndrome:</i> 2.70 at 20-70+y	409 at 20-70+y	Not reported
Patja et al (2008) ¹⁰	Finland	<i>M:</i> 2.2 at 20-39y, 1.0 at 40-59y, 1.0 at 60+y <i>F:</i> 1.4 at 20-39y, 1.1 at 40-49y, 1.0 at 60+y <i>Mild ID:</i> <i>M:</i> 1.6 at 20-39y, 1.0 at 40-59y, 1.0 at 60+y <i>F:</i> 1.2 at 20-39y, 1.1 at 40-49y, 1.0 at 60+y	1,046 at 20-97y	<i>Underlying cause at 2-97y:</i> Vascular: 36% (cardiac infarct 33%, cerebral infarct 33%, congenital heart disease 18%, pulmonary infarct 6%) Respiratory: 22% (pneumonia 83%, COPD 11%)

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		<p><i>Moderate ID:</i> M: 2.3 at 20-39y, 1.1 at 40-59y, 1.0 at 60+y F: 1.5 at 20-39y, 1.1 at 40-49y, 1.0 at 60+y</p> <p><i>Severe ID:</i> M: 2.6 at 20-39y, 1.2 at 40-59y, 1.0 at 60+y F: 1.6 at 20-39y, 1.0 at 40-49y, 1.0 at 60+y</p> <p><i>Profound ID:</i> M: 2.1 at 20-39y, 1.1 at 40-59y, 1.0 at 60+y F: 1.3 at 20-39y, 1.2 at 40-49y, 1.0 at 60+y</p>		<p>Neoplasm: 11% (digestive 44%, respiratory 15%, urogenital, 12%) Digestive: 7% (intestinal obstruction 25%, ulcer perforation 13%) Accidents and poisonings: 7% (commonest was fatal fracture, then drowning) Vascular, neoplasm, and accident causes were less common than sex-age-matched general population; Digestive were 2.5 times, Respiratory 2.6-5.8 times more common</p>
Tyrer & McGoher (2009) ¹¹	England	<p>2.77 (2.53, 3.03) at 20+y M: 2.28 (2.02, 2.56) at 20+y F: 3.24 (2.83, 3.69) at 20+y</p>	503 at 20+y	<p><i>Underlying cause at 20+y:</i> Pneumonia: 13.1%, SMR=6.47 (5.00, 8.23) Nervous system: 13.1%, SMR=16.30 (12.61, 20.74) Other respiratory: 12.9%, SMR=4.64 (3.58, 5.91) Ischaemic heart disease: 11.5%, SMR=1.49 (1.13, 1.92) Neoplasm: 9.3% Congenital anomalies: 9.1%, SMR=85.60 (62.67, 114.18) Cerebrovascular disease: 7.8%, SMR=2.40 (1.71, 3.28)</p>
Oullette-Kuntz et al (2015) ¹²	Canada	<p>2.5 (2.1, 2.9) at 0-60+y M: 2.1 (1.7, 2.6) at 0-60+y F: 3.0 (2.4, 3.8) at 0-60+y M: 1.7 (1.3, 2.3) to 3.4 (2.3, 4.7) at 20-60+y F: 2.1 (1.4, 2.9) to 6.1 (4.1, 8.6) at 20-60+y</p>	172 at 0-60+y; 158 at 20-60+y	<p><i>Risk factors for death:</i> Age, Down syndrome (OR=1.76 at 20-39y; OR=1.69 at 40-59y; OR=22.34 at 60+y), cerebral palsy (OR=2.39 at 20-39y; OR=0.93 at 40-59y; OR=0.50 at 60+y), blindness/low vision (OR not given), technological dependence/medical fragility (OR=11.96 at 20-39y; OR=7.28 at 40-59y; OR=3.42 at 60+y), wheelchair dependence (OR=5.96 at 20-39y; OR=2.89 at 40-59y; OR=2.56 at 60+y), mobility impairment without wheelchair dependence (OR not given), epilepsy (OR=1.83 at 20-39y; OR=1.80 at 40-59y; OR=1.09 at 60+y)</p>
Florio & Troller (2015) ¹³	Australia	<p>2.48 (2.32, 2.64) at 0-85+y 3.15 (2.94, 3.38) at 5-69y M: 2.52 (2.29, 2.77) at 5-69y F: 4.26 (3.83, 4.74) at 5-69y</p>	953 at 0-85+y; 831 at 15+y	Not reported
McCarron et al (2015) ¹⁴	Republic of Ireland	<p>3.85 (3.70, 4.00) at 0-80+y M: 3.09 (2.93, 3.25) at 0-80+y F: 4.90 (4.63, 5.17) at 0-80+y 2.71 (2.41, 3.04) to 6.09 (5.29, 6.96) at 20-80y M: 2.50 (2.18, 2.86) to 4.50 (3.69, 5.44) at 20-80y F: 2.71 (2.32, 3.14) to 10.07 (8.99, 13.10) at 20-80y</p>	2,666 at 0-80+y; 2,394 at 20-80+y	Not reported

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1 2 3 4	Heslop & Glover (2015) ¹⁵	England	Median 2.13 (interquartile range 1.09, 2.83) across geographic areas at 18-65+y	18-65+y	Not reported
5 6 7 8 9 10 11 12 13 14	Arvio et al (2016) ¹⁶	Finland	<i>Mild ID:</i> 2.28 (2.18, 2.39) at 0-60+y 1.99 (1.85, 2.13) to 2.77 (2.36, 3.23) at 15-60+y <i>M:</i> 2.01 (1.88, 2.14) at 0-60+y <i>F:</i> 2.80 (2.60, 3.01) at 0-60+y <i>Severe ID:</i> 3.41 (3.30, 3.52) at 0-60+y 2.07 (1.96, 2.19) to 8.77 (7.77, 9.87) at 15-60+y <i>M:</i> 2.59 (2.48, 2.72) at 0-60+y <i>F:</i> 5.24 (4.99, 5.50) at 0-60+y	5,171 at 0-60+y; 5,053 at 15-60y	Not reported
15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32	Hosking et al (2016) ⁵	England	HR=3.62 (3.33, 3.93) at 18-84y <i>M:</i> HR=3.30 (2.96, 3.68) at 18-84y <i>F:</i> HR=4.10 (3.61, 4.66) at 18-84y <i>With Down syndrome:</i> HR=9.21 (7.22, 11.76) <i>Without Down syndrome:</i> HR=3.19 (2.92, 3.49) <i>With epilepsy:</i> HR=6.04 (5.04, 7.24) <i>Without epilepsy:</i> HR=3.18 (2.90, 3.50) <i>With high level of support needs:</i> HR=4.77 (4.08, 5.59) <i>Without high level of support needs:</i> HR=3.28 (2.98, 3.62) <i>With autism:</i> HR=2.39 (1.45, 3.96) <i>Without autism:</i> HR=3.66 (3.37, 3.98) <i>In communal/shared homes:</i> HR=4.99 (4.36, 5.73) <i>Not in communal/shared homes:</i> HR=3.05 (2.74, 3.30)	656 at 18-84y	<i>Underlying cause at 18-84y:</i> Circulatory: 21.6%, HR=3.05 (2.56, 3.64) Respiratory: 18.8% (pneumonia and aspiration pneumonia), HR=6.68 (5.38, 8.29) Neoplasm: 14.9%, HR=1.44 (1.18, 1.76) Nervous system: 11.6%, HR=13.79 (9.70, 19.62) Digestive: 7.0%, HR=4.02 (2.92, 5.54) Congenital anomalies: 6.9%, HR could not be estimated Mental disorders: 5.3%, HR=7.99 (5.19, 12.31) External causes: 4.1%, HR=1.85 (1.26, 2.71) Genitourinary: 3.5%, HR=10.89 (6.09, 19.47) Endocrine, nutritional, and metabolic: 2.0%, HR=5.38 (2.79, 10.07) <i>Down syndrome:</i> Respiratory: 20.3% (or 42.4% if "Down syndrome" is excluded as an underlying cause of death) <i>Avoidable deaths:</i> 37% amenable (23% controls), 19% preventable (40% controls)
33 34 35 36 37 38 39 40 41 42	Lauer (2016) ¹⁷	USA	Not reported	438 in 2012, 409 in 2013, at 18+y	<i>Major cause of death, 2012, 2013</i> Heart disease: 16.0%, 13.7% Neoplasm: 13.7%, 13.4% Alzheimer disease: 13.0%-12.2% (48% in Down syndrome) Aspiration pneumonia: 9.4%, 8.6% Septicaemia: 10.0%, 8.6% Chronic lower respiratory diseases: 4.6%, 6.6% Unintentional injury: 4.8%, 3.2%

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Troller et al (2017) ¹⁸	Australia	1.3 (1.2, 1.5) at 20+y 4.0 (3.1, 5.2) at 20-44y 2.3 (2.0, 2.7) at 45-64y 1.0 (0.8, 1.2) at 65+y M: 1.4 (1.1, 1.6) at 20+y F: 1.3 (1.1, 1.6) at 20+y	732 at 20-65+y	<p><i>Underlying cause at 20-65+y:</i></p> <p>Circulatory: 18%</p> <p>Neoplasm: 18%</p> <p>Nervous: 16%</p> <p>Respiratory: 12%</p> <p>Congenital anomaly: 11%</p> <p>Injury and poisoning: 6%</p> <p>Digestive: 5%</p> <p><i>Avoidable deaths: 31%</i></p>
Glover et al (2017) ⁶	England	3.18 (2.94, 3.43) at 0-99y M: 3.03 (2.73, 3.35) at 0-99y F: 3.40 (3.02, 3.81) at 0-99y 1.6 (1.2, 2.1) to 7.8 (5.4, 11.1) at 18-99y M: 1.5 (0.9, 2.2) to 6.6 (4.0, 10.1) at 18-99y F: 1.7 (1.1, 2.4) to 11.6 (6.0, 20.2) at 18-99y	664 at 0-99y	<p><i>Underlying cause at 0-99y:</i></p> <p>Circulatory: 22.9% (ischaemic heart disease 37.5%, cerebrovascular 25.7%, thrombophlebitis 6.6%, cardiomyopathy 5.9%, PE 3.9%), SMR=2.8 (2.4, 3.3)</p> <p>Respiratory: 17.2% (pneumonia 50.0%, pneumonitis 21.0%), SMR=4.9 (4.0, 5.9)</p> <p>Neoplasm: 3.1% (digestive 36.8%, respiratory 13.8%, female genital tract 10.3%, lymphoid and haematopoietic 10.3%), SMR=1.1 (0.9, 1.4)</p> <p>Nervous: 12.8%, SMR=9.8 (7.8, 12.1)</p> <p>Congenital anomalies: 8.4%, SMR=72.9 (55.1, 94.7)</p> <p>Digestive: 7.8%, SMR=4.0 (3.0, 5.2)</p> <p>No ICD10 chapters had fewer than expected deaths</p> <p>Other common single causes: dementia 33/664, epilepsy 26/664, cerebral palsy 23/664</p> <p><i>Avoidable deaths:</i></p> <p>44.7% (41.0%, 48.5%), mostly amenable</p> <p>M: 50.9% (45.9%, 56.0%); F: 36.9% (31.5%, 42.5%)</p>

COPD=chronic obstructive pulmonary disease; HR=hazard ratio; ID=intellectual disabilities; OR=odds ratio; PE=pulmonary embolism; SMR=standardised mortality ratio; y=years

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Supplementary table 2. Groupings of related causes of deaths

Infectious diseases

Infection

ENTEROCOLITIS DUE TO CLOSTRIDIUM DIFFICILE
 SEPSIS DUE TO STAPHYLOCOCCUS AUREUS
 SEPSIS, UNSPECIFIED
 BACTERIAL INFECTION, UNSPECIFIED
 SUBACUTE SCLEROSING PANENCEPHALITIS
 CHRONIC VIRAL HEPATITIS B WITHOUT DELTA-AGENT
 PULMONARY CANDIDIASIS
 NECROTISING FASCIITIS
 URINARY TRACT INFECTION, SITE NOT SPECIFIED

Neoplasms

Gastrointestinal malignant neoplasms

MALIGNANT NEOPLASM OF PAROTID GLAND
 MALIGNANT NEOPLASM, OESOPHAGUS, UNSPECIFIED
 MALIGNANT NEOPLASM, STOMACH, UNSPECIFIED
 MALIGNANT NEOPLASM, CAECUM
 MALIGNANT NEOPLASM, SIGMOID COLON
 MALIGNANT NEOPLASM, COLON, UNSPECIFIED
 INTRAHEPATIC BILE DUCT CARCINOMA
 NEOPLASM OF UNCERTAIN OR UNKNOWN BEHAVIOUR, OTHER DIGESTIVE ORGANS

Other neoplasms

MALIGNANT NEOPLASM, LOWER LOBE, BRONCHUS OR LUNG
 MALIGNANT NEOPLASM, BRONCHUS OR LUNG, UNSPECIFIED
 MALIGNANT NEOPLASM, BREAST, UNSPECIFIED
 MALIGNANT NEOPLASM, ENDOMETRIUM
 MALIGNANT NEOPLASM OF OVARY
 MALIGNANT NEOPLASM, TESTIS, UNSPECIFIED
 MALIGNANT NEOPLASM, BLADDER, UNSPECIFIED
 MALIGNANT NEOPLASMS OF THYROID GLAND
 WALDENSTROM MACROGLOBULINAEMIA
 NON-HODGKIN'S LYMPHOMA, UNSPECIFIED
 MALIGNANT NEOPLASM OF UNSPECIFIED SITE
 NEOPLASM OF UNCERTAIN OR UNKNOWN BEHAVIOUR, TRACHEA, BRONCHUS AND LUNG
 SECONDARY MALIGNANT NEOPLASM OF LUNG
 SECONDARY MALIGNANT NEOPLASM OF LIVER AND INTRAHEPATIC BILE DUCT
 SECONDARY MALIGNANT NEOPLASM OF BRAIN AND CEREBRAL MENINGES
 SECONDARY MALIGNANT NEOPLASM OF OTHER SPECIFIED SITES

Endocrine and metabolic diseases

Diabetes

INSULIN-DEPENDENT DIABETES MELLITUS WITHOUT COMPLICATIONS
 NON-INSULIN-DEPENDENT DIABETES MELLITUS WITH RENAL COMPLICATIONS
 NON-INSULIN-DEPENDENT DIABETES MELLITUS W. PERIPHERAL CIRC. COMPLICATIONS
 NON-INSULIN-DEPENDENT DIABETES MELLITUS WITHOUT COMPLICATIONS
 UNSPECIFIED DIABETES MELLITUS WITH RENAL COMPLICATIONS

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1
2 UNSPECIFIED DIABETES MELLITUS WITHOUT COMPLICATIONS
3 ABNORMAL GLUCOSE TOLERANCE TEST
4 HYPERGLYCAEMIA, UNSPECIFIED

6 **Metabolic disorders**

7 OTHER HYPERPHENYLALANINAEMIAS
8 DISORDERS OF PHOSPHORUS METABOLISM & PHOSPHATASES
9 DISORDERS OF PLASMA-PROTEIN METABOLISM, NOT ELSEWHERE CLASSIFIED

12 **Mental disorders**

13 **Dementias**

14 VASCULAR DEMENTIA, UNSPECIFIED
15 UNSPECIFIED DEMENTIA
16 ALZHEIMER'S DISEASE WITH LATE ONSET
17 ALZHEIMER'S DISEASE, UNSPECIFIED

19 **Mental health**

20
21 MENTAL AND BEHAVIOURAL DISORDERS DUE TO ACUTE INTOXICATION WITH ALCOHOL
22 MENTAL AND BEHAVIOURAL DISORDERS DUE TO ALCOHOL DEPENDENCE SYNDROME
23 MENTAL AND BEHAVIOURAL DISORDERS DUE TO USE OF TOBACCO, UNSPECIFIED
24 SCHIZOPHRENIA, UNSPECIFIED
25 BIPOLAR AFFECTIVE DISORDER, UNSPECIFIED
26 OTHER & UNSPEC SYMPTOMS & SIGNS INVOLVING COGNITIVE FUNCTIONS & AWARENESS
27 INTENTIONAL SELF-HARM BY JUMPING FROM A HIGH PLACE

29 **Intellectual disabilities**

30
31 UNSPECIFIED MENTAL RETARDATION
32 DEVELOPMENTAL DISORDER OF SCHOLASTIC SKILLS, UNSPECIFIED

34 **Nervous system**

35 **Epilepsies**

36
37 GENERALIZED IDIOPATHIC EPILEPSY AND EPILEPTIC SYNDROMES
38 EPILEPSY, UNSPECIFIED
39 STATUS EPILEPTICUS, UNSPECIFIED
40 MYOTONIC DISORDERS
41 OTHER AND UNSPECIFIED CONVULSIONS

43 **Cerebral palsy**

44 SPASTIC QUADRAPLEGIC CEREBRAL PALSY
45 SPASTIC HEMIPLEGIC CEREBRAL PALSY
46 OTHER CEREBRAL PALSY
47 CEREBRAL PALSY, UNSPECIFIED
48 TETRAPLEGIA, UNSPECIFIED

51 **Other neurological conditions**

52 SEQUELAE OF INFLAMMATORY DISEASES OF CENTRAL NERVOUS SYSTEM
53 PARKINSON'S DISEASE
54 MYONEURAL DISORDER, UNSPECIFIED
55 ENCEPHALITIS, MYELITIS AND ENCEPHALOMYELITIS, UNSPECIFIED
56 ANOXIC BRAIN DAMAGE, NOT ELSEWHERE CLASSIFIED
57 BLINDNESS, BINOCULAR
58 OTHER DISORDERS OF NERVOUS SYSTEM, NOT ELSEWHERE CLASSIFIED
59
60

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Circulatory system

Acute myocardial infarction

ACUTE MYOCARDIAL INFARCTION, UNSPECIFIED

CARDIAC ARREST, UNSPECIFIED

Other ischaemic heart disease

HYPERTENSIVE HEART DISEASE WITHOUT (CONGESTIVE) HEART FAILURE

ACUTE ISCHAEMIC HEART DISEASE, UNSPECIFIED

ATHEROSCLEROTIC HEART DISEASE

CHRONIC ISCHAEMIC HEART DISEASE, UNSPECIFIED

ATHEROSCLEROSIS OF AORTA

GENERALIZED AND UNSPECIFIED ATHEROSCLEROSIS

Heart failure

HEART FAILURE, UNSPECIFIED

LEFT VENTRICULAR FAILURE

CONGESTIVE HEART FAILURE

Other cardiovascular disease

PULMONARY EMBOLISM WITHOUT MENTION OF ACUTE COR PULMONALE

OTHER SPECIFIED PULMONARY HEART DISEASES

PULMONARY HEART DISEASE, UNSPECIFIED

AORTIC (VALVE) STENOSIS

ATRIAL FIBRILLATION AND FLUTTER

VENTRICULAR FIBRILLATION AND FLUTTER

OTHER ILL-DEFINED HEART DISEASES

PULMONARY OEDEMA

CARDIOGENIC SHOCK

PERIPHERAL VASCULAR DISEASE, UNSPECIFIED

PHLEBITIS AND THROMBOPHLEBITIS OF OTHER DEEP VESSELS OF LOWER EXTREMITIES

EMBOLISM AND THROMBOSIS OF OTHER SPECIFIED VEINS

ACUTE AND SUBACUTE INFECTIVE ENDOCARDITIS

ACUTE ENDOCARDITIS, UNSPECIFIED

ENDOCARDITIS, VALVE UNSPECIFIED

DILATED CARDIOMYOPATHY

CARDIOMEGALY

ESSENTIAL (PRIMARY) HYPERTENSION

Stroke

INTRACEREBRAL HAEMORRHAGE, UNSPECIFIED

CEREBRAL INFARCTION DUE TO THROMBOSIS OF PRECEREBRAL ARTERIES

CEREBRAL INFARCTION DUE TO UNSPECIFIED OCCLUSION/STENOSIS OF PRECEREBRAL ARTERIES

CEREBRAL INFARCTION, UNSPECIFIED

STROKE, NOT SPECIFIED AS HAEMORRHAGE OR INFARCTION

CEREBROVASCULAR DISEASE, UNSPECIFIED

SEQUELAE OF STROKE, NOT SPECIFIED AS HAEMORRHAGE OR INFARCTION

SEQUELAE OF OTHER AND UNSPECIFIED CEREBROVASCULAR DISEASES

Respiratory system

Respiratory infection

ACUTE UPPER RESPIRATORY INFECTION, UNSPECIFIED

INFLUENZA WITH PNEUMONIA, OTHER INFLUENZA VIRUS IDENTIFIED

INFLUENZA WITH OTHER RESPIRATORY MANIFESTATIONS, OTHER INFLUENZA VIRUS IDENTIFIED

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1
2 PNEUMONIA DUE TO STREPTOCOCCUS PNEUMONIAE
3 BRONCHOPNEUMONIA, UNSPECIFIED
4 LOBAR PNEUMONIA, UNSPECIFIED
5 HYPOSTATIC PNEUMONIA, UNSPECIFIED
6 PNEUMONIA, UNSPECIFIED
7 UNSPECIFIED ACUTE LOWER RESPIRATORY INFECTION
8 CHRONIC OBSTRUCTIVE PULMONARY DISEASE WITH ACUTE LOWER RESP INFECTION
9
10

Aspiration/reflux/choking

11 PNEUMONITIS DUE TO FOOD AND VOMIT
12 GASTRO-OESOPHAGEAL REFLUX DISEASE WITHOUT OESOPHAGITIS
13 INHALATION AND INGESTION OF FOOD CAUSING OBSTRUCTION OF RESPIRATORY TRACT
14 FOREIGN BODY IN RESPIRATORY TRACT, PART UNSPECIFIED
15 INHALATION/INGESTION OF OTHER OBJECTS CAUSING OBSTRUCT OF RESP TRACT
16
17
18

Other respiratory disorders

19 UNSPECIFIED CHRONIC BRONCHITIS
20 EMPHYSEMA, UNSPECIFIED
21 CHRONIC OBSTRUCTIVE PULMONARY DISEASE, UNSPECIFIED
22 ASTHMA, UNSPECIFIED
23 BRONCHIECTASIS
24 OTHER INTERSTITIAL PULMONARY DISEASES WITH FIBROSIS
25 PLEURAL EFFUSION, NOT ELSEWHERE CLASSIFIED
26 CHRONIC RESPIRATORY FAILURE
27 RESPIRATORY FAILURE, UNSPECIFIED
28 OTHER SPECIFIED RESPIRATORY DISORDERS
29 DYSPNOEA
30 RESPIRATORY ARREST
31 ASPHYXIATION
32 UNSPECIFIED THREAT TO BREATHING
33
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Digestive system

Ulcer/gastrointestinal perforation

38 OESOPHAGITIS
39 PERFORATION OF INTESTINE (NONTRAUMATIC
40 PERITONITIS, UNSPECIFIED
41 GASTRIC ULCER, CHRONIC OR UNSPECIFIED WITH PERFORATION
42 OTHER PERITONITIS
43 ACUTE PERITONITIS
44 GASTROINTESTINAL HAEMORRHAGE, UNSPECIFIED
45 ULCER OF INTESTINE
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Other gastrointestinal disorders

51 BARRETTS OESOPHAGUS
52 DIAPHRAGMATIC HERNIA WITHOUT OBSTRUCTION OR GANGRENE
53 OTHER SPECIFIED NONINFECTIVE GASTROENTERITIS AND COLITIS
54 ACUTE VASCULAR DISORDERS OF INTESTINE
55 VASCULAR DISORDER OF INTESTINE, UNSPECIFIED
56 VOLVULUS
57 OTHER AND UNSPECIFIED INTESTINAL OBSTRUCTION
58 CONSTIPATION
59 MEGACOLON, NOT ELSEWHERE CLASSIFIED
60

Rates, causes, place, and predictors of mortality in adults with intellectual disabilities with and without Down syndrome: cohort study with record linkage

1
2 ACUTE AND SUBACUTE HEPATIC FAILURE
3 OTHER AND UNSPECIFIED CIRRHOSIS OF LIVER
4 AUTOIMMUNE HEPATITIS
5 INFLAMMATORY LIVER DISEASE, UNSPECIFIED
6 OTHER SPECIFIED DISEASES OF LIVER
7 CALCULUS OF GALLBLADDER WITH OTHER CHOLECYSTITIS
8 CHOLANGITIS
9 ACUTE PANCREATITIS, UNSPECIFIED
10 PSEUDOCYST OF PANCREAS
11 INTESTINAL MALABSORPTION, UNSPECIFIED
12 DYSPHAGIA
13
14
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Genitourinary system

Renal failure

16
17
18
19 CHRONIC NEPHRITIC SYNDROME, UNSPECIFIED
20 OTHER ACUTE RENAL FAILURE
21 ACUTE RENAL FAILURE, UNSPECIFIED
22 END-STAGE RENAL DISEASE
23 CHRONIC KIDNEY DISEASE, STAGE 5
24 CHRONIC KIDNEY DISEASE, UNSPECIFIED
25 UNSPECIFIED KIDNEY FAILURE
26
27
28

Chromosomal abnormalities

Down syndrome

29
30
31
32 DOWN'S SYNDROME, UNSPECIFIED
33

Other congenital condition

34 CONGENITAL HYDROCEPHALUS, UNSPECIFIED
35 SPINA BIFIDA, UNSPECIFIED
36 CONGENITAL MALFORMATION OF HEART, UNSPECIFIED
37 CONGENITAL DEFORMITY OF SPINE
38 CONGEN MALFORMATION SYNDROMES PREDOMINANTLY ASSOCIATED WITH SHORT
39 STATURE
40 MARFAN'S SYNDROME
41 OTHER SPECIFIED CONGEN MALFORMATION SYNDROMES, NOT ELSEWHERE CLASSIFIED
42 CONGENITAL MALFORMATION, UNSPECIFIED
43 KLINEFELTER'S SYNDROME, UNSPECIFIED
44 FRAGILE X CHROMOSOME
45 OTHER LACK OF EXPECTED NORMAL PHYSIOLOGICAL DEVELOPMENT
46
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Other conditions occurring with small frequency

Other condition

50
51
52 DECUBITUS ULCER AND PRESSURE AREA
53 SCOLIOSIS, UNSPECIFIED
54 URETHRAL STRICTURE, UNSPECIFIED
55 EPISTAXIS
56 IMMOBILITY
57 MALAISE AND FATIGUE
58 GENERALIZED ENLARGED LYMPH NODES
59 INSUFFICIENT INTAKE OF FOOD AND WATER DUE TO SELF NEGLECT
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Rates, causes, place, and predictors of mortality in adults with intellectual disabilities with and without Down syndrome: cohort study with record linkage

1
2 OTHER SPECIFIED GENERAL SYMPTOMS AND SIGNS
3 OTHER ILL-DEFINED AND UNSPECIFIED CAUSES OF MORTALITY
4 EXPOSURE TO UNSPECIFIED FACTOR
5 MULTI-SYSTEM DEGENERATION
6 BENIGN NEOPLASM, MENINGES, UNSPECIFIED
7 AGRANULOCYTOSIS
8 SARCOIDOSIS OF OTHER AND COMBINED SITES
9 SARCOIDOSIS, UNSPECIFIED
10 HYPOPITUITARISM
11 HYPOTHYROIDISM, UNSPECIFIED
12 OTHER THYROTOXICOSIS
13 VOLUME DEPLETION
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Injuries and external causes

Injuries and accidents

18
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21 INTRACRANIAL INJURY, UNSPECIFIED
22 UNSPECIFIED INJURY OF HEAD
23 INJURY OF COLON
24 FRACTURE OF NECK OF FEMUR
25 FRACTURE OF SHAFT OF TIBIA
26 UNSPECIFIED MULTIPLE INJURIES
27 FAT EMBOLISM (TRAUMATIC)
28 SEQUELAE OF UNSPECIFIED INJURY OF HEAD
29 UNSPECIFIED FALL
30 SEQUELAE OF OTHER ACCIDENTS
31
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33

Medical/surgical complication

34 POISONING BY OTHER ANTIDYSRHYTHMIC DRUGS, NOT ELSEWHERE CLASSIFIED
35 ADVERSE EFFECTS OF OTHER ANTIDYSRHYTHMIC DRUGS, NOT ELSEWHERE CLASSIFIED
36 ABN REACT TO/LATER COMPLIC OF OP WITH IMPLANT OF ARTIFICIAL INTERN DEVICE
37 ABN REACT TO/LATER COMPLIC OF OP WITH ANASTOMOSIS, BYPASS OR GRAFT
38 ABN REACT TO/LATER COMPLIC OF OP WITH FORMATION OF EXTERNAL STOMA
39 ABNORMAL REACTION TO OR LATER COMPLICATION OF OTHER MEDICAL PROCEDURES
40 SEQ OF PROCED CAUSING ABN REACT/COMPLIC,W/O MENTION OF MISADV AT THE TIME
41 OTHER POSTPROCEDURAL RESPIRATORY DISORDERS
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Rates, causes, place, and predictors of mortality in adults with intellectual disabilities with and without Down syndrome: cohort study with record linkage

Supplementary table 3. Predictors of the outcome time to death from univariate analyses

Variable		N with event/ N in group	Hazard ratio (95% CI)	Individual p-value	Overall p-value
Demographics					
Age		294/961	1.05 (1.04, 1.06)	<0.0001	
Sex	Male	154/525	0.88 (0.70, 1.11)	0.2730	
	Female	140/436	1.00 (-)		
Ability level	Mild ID	92/382	1.00 (-)		0.0007
	Moderate ID	73/236	1.38 (1.01, 1.87)	0.0411	
	Severe ID	67/180	1.75 (1.28, 2.40)	0.0005	
	Profound ID	62/163	1.77 (1.28, 2.45)	0.0005	
Type of accommodation	Family carer	70/374	1.00 (-)		<0.0001
	Independent of care	36/93	2.35 (1.57, 3.52)	<0.0001	
	Paid support	161/435	2.18 (1.65, 2.88)	<0.0001	
	Congregate	27/59	2.87 (1.84, 4.48)	<0.0001	
Neighbourhood deprivation	1 - most affluent	18/73	1.00 (-)		0.1890
	2	56/137	1.92 (1.13, 3.27)	0.0158	
	3	10/45	0.90 (0.42, 1.95)	0.7896	
	4	10/40	1.06 (0.49, 2.30)	0.8808	
	5	12/32	1.71 (0.82, 3.55)	0.1527	
	6	9/32	1.27 (0.57, 2.82)	0.5640	
	7	9/34	1.09 (0.49, 2.43)	0.8302	
	8	15/58	1.21 (0.61, 2.41)	0.5818	
	9	35/124	1.22 (0.69, 2.16)	0.4882	
	10 - most deprived	120/386	1.41 (0.86, 2.31)	0.1782	
Civil status	Single	288/938	1.28 (0.57, 2.87)	0.5485	
	Not single	6/23	1.00 (-)		
Employment/day activities	Yes	83/231	1.33 (1.03, 1.71)	0.0284	
	No	211/730	1.00 (-)		
Smoker	Yes	46/101	1.70 (1.24, 2.33)	0.0009	
	No	248/860	1.00 (-)		
Down syndrome	Yes	64/179	1.30 (0.98, 1.71)	0.0673	
	No	230/782	1.00 (-)		
Epilepsy	Yes	111/325	1.25 (0.99, 1.58)	0.0636	
	No	183/636	1.00 (-)		
Spastic quadriplegia	Yes	24/325	1.67 (1.10, 2.54)	0.0158	
	No	183/636	1.00 (-)		
Impaired mobility	Yes	195/735	0.51 (0.40, 0.65)	<0.0001	
	No	99/226	1.00 (-)		
Body mass index	Underweight	9/43	0.63 (0.32, 1.25)	0.1847	0.1865
	Acceptable	83/265	1.00 (-)		
	Overweight	75/289	0.78 (0.57, 1.06)	0.1132	
	Obese	81/237	1.08 (0.80, 1.47)	0.6152	
	Morbidly obese	16/58	0.87 (0.51, 1.48)	0.6058	
Hearing impairment	Yes	112/267	1.79 (1.41, 2.26)	<0.0001	
	No	182/694	1.00 (-)		
Visual impairment	Yes	154/449	1.29 (1.02, 1.62)	0.0317	
	No	140/512	1.00 (-)		

Rates, causes, place, and predictors of mortality in adults with intellectual disabilities with and without Down syndrome: cohort study with record linkage

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Urinary incontinence	Yes	158/632	0.52 (0.41, 0.65)	<0.0001	
	No	136/329	1.00 (-)		
Bowel incontinence	Yes	197/733	0.55 (0.43, 0.70)	<0.0001	
	No	97/228	1.00 (-)		
Diabetes	Yes	29/47	2.72 (1.86, 4.00)	<0.0001	
	No	265/914	1.00 (-)		
PEG/tube fed	Yes	N/7	4.99 (2.22, 11.20)	0.0001	
	No	288/954			
Constipation	Yes	112/316	1.34 (1.06, 1.70)	0.0145	
	No	182/645	1.00 (-)		
Ataxia/gait disorder	Yes	104/276	1.50 (1.18, 1.90)	0.0009	
	No	190/685	1.00 (-)		
Nail disorder	Yes	74/223	1.18 (0.91, 1.54)	0.2120	
	No	220/738	1.00 (-)		
Epidermal thickening	Yes	66/207	1.10 (0.84, 1.45)	0.4947	
	No	228/754	1.00 (-)		
Cerebral palsy	Yes	54/175	1.02 (0.76, 1.37)	0.8792	
	No	240/786	1.00 (-)		
Osteoporosis	Yes	76/174	1.71 (1.32, 2.22)	<0.0001	
	No	218/786	1.00 (-)		
Fungal infection	Yes	42/158	0.83 (0.61, 1.18)	0.3366	
	No	252/803	1.00 (-)		
Hypertension	Yes	56/146	1.36 (1.01, 1.82)	0.0399	
	No	238/815	1.00 (-)		
Dysphagia	Yes	51/132	1.51 (1.11, 2.04)	0.0080	
	No	243/829	1.00 (-)		
Dyspnoea	Yes	49/130	1.41 (1.04, 1.92)	0.0285	
	No	245/831	1.00 (-)		
Musculoskeletal pain	Yes	48/148	1.14 (0.83, 1.55)	0.4153	
	No	246/813	1.00 (-)		
Bone deformity	Yes	50/139	1.32 (0.97, 1.79)	0.0769	
	No	244/822	1.00 (-)		
Dental/oral problem	Yes	38/120	1.07 (0.76, 1.50)	0.7128	
	No	256/841	1.00 (-)		
Eczema/dermatitis	Yes	38/138	0.86 (0.61, 1.21)	0.3790	
	No	256/823	1.00 (-)		
GORD	Yes	51/133	1.43 (1.06, 1.94)	0.0198	
	No	243/828	1.00 (-)		
Lower respiratory tract infection	Yes	55/126	1.75 (1.30, 2.34)	0.0002	
	No	239/835	1.00 (-)		
Total number of physical conditions		294/961	1.06 (1.04, 1.08)	<0.0001	
Psychosis	Yes	11 /42	0.81 (0.44, 1.48)	0.4990	
	No	283 /919	1.00 (-)		
Affective disorder including bipolar	Yes	24/68	1.19 (0.78, 1.80)	0.4216	
	No	270/893	1.00 (-)		
Autism	Yes	13/69	0.54 (0.31, 0.94)	0.0306	
	No	281/892	1.00 (-)		
Problem behaviour	Yes	71/218	1.09 (0.83, 1.42)	0.5251	
	No	223/743	1.00 (-)		
Eating disorder, including pica	Yes	5/17	0.99 (0.41, 2.40)	0.9857	
	No	289/944	1.00 (-)		
Any mental illness, excluding problem behaviours	Yes	73/217	1.16 (0.89, 1.51)	0.2849	
	No	221/744	1.00 (-)		
Service use					
Number of GP consultations in last 12 months		287/951	1.05 (1.03, 1.06)	<0.0001	

Rates, causes, place, and predictors of mortality in adults with intellectual disabilities with and without Down syndrome: cohort study with record linkage

Number of A&E attendances in last 12 months		280/938	1.09 (0.99, 1.20)	0.0847	
Number of health professions providing care		294/961	1.10 (1.03, 1.16)	0.0023	
Prescriptions					
Antipsychotics	Yes	79/226	1.12 (0.94, 1.57)	0.1421	
	No	215/735	1.00 (-)		
Antidepressants	Yes	39/118	1.16 (0.83, 1.63)	0.3778	
	No	255/843	1.00 (-)		
Anxiolytic/hypnotics	Yes	20/68	0.95 (0.60, 1.49)	0.8159	
	No	274/893	1.00 (-)		
Antiepileptics	Yes	90/253	1.31 (1.02, 1.68)	0.0315	
	No	204/708	1.00 (-)		
Number of drug classes taken		294/961	1.16 (1.12, 1.21)	<0.0001	

A&E=accident and emergency; CI=confidence interval; GORD=gastro-oesophageal reflux disorder; PEG=percutaneous endoscopic gastrostomy

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No.	Recommendation	Page No.	Relevant text from manuscript
Title and abstract	1	(a) Indicate the study’s design with a commonly used term in the title or the abstract		p1
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found		p2
Introduction				
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported		p4-6, supplementary table 1
Objectives	3	State specific objectives, including any prespecified hypotheses		6, paragraph 3
Methods				
Study design	4	Present key elements of study design early in the paper		p6-10, supplementary tables 2/3
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection		p7, paragraph 1, 7-8
Participants	6	(a) <i>Cohort study</i> —Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up <i>Case-control study</i> —Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls <i>Cross-sectional study</i> —Give the eligibility criteria, and the sources and methods of selection of participants		p7, paragraph 1
		(b) <i>Cohort study</i> —For matched studies, give matching criteria and number of exposed and unexposed <i>Case-control study</i> —For matched studies, give matching criteria and the number of controls per case		p7, paragraph 2, p9, paragraph 4
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable		p7-8, supplementary table 2
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group		p7-8, p9, paragraph 4
Bias	9	Describe any efforts to address potential sources of bias		p9, paragraph 4
Study size	10	Explain how the study size was arrived at		P7, paragraph2, p9, paragraph 4

Continued on next page

Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	p8-10
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	p8-10
		(b) Describe any methods used to examine subgroups and interactions	p8-10
		(c) Explain how missing data were addressed	p11, paragraph 2
		(d) <i>Cohort study</i> —If applicable, explain how loss to follow-up was addressed	p11, paragraph 2
		<i>Case-control study</i> —If applicable, explain how matching of cases and controls was addressed	
		<i>Cross-sectional study</i> —If applicable, describe analytical methods taking account of sampling strategy	
		(e) Describe any sensitivity analyses	N/A
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	p11, paragraph 2
		(b) Give reasons for non-participation at each stage	p11, paragraph 2
		(c) Consider use of a flow diagram	-
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	p11-12, Table 1, supplementary table 3
		(b) Indicate number of participants with missing data for each variable of interest	table 1, supplementary table 3
		(c) <i>Cohort study</i> —Summarise follow-up time (eg, average and total amount)	p12, paragraph 1
Outcome data	15*	<i>Cohort study</i> —Report numbers of outcome events or summary measures over time	p11, paragraph 2
		<i>Case-control study</i> —Report numbers in each exposure category, or summary measures of exposure	
		<i>Cross-sectional study</i> —Report numbers of outcome events or summary measures	
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	P15, table 6
		(b) Report category boundaries when continuous variables were categorized	N/A
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	-

Continued on next page

Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	p11-16
Discussion			
Key results	18	Summarise key results with reference to study objectives	p16, paragraph 2
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	p20, paragraph 1
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	p20, paragraph 2
Generalisability	21	Discuss the generalisability (external validity) of the study results	p20, paragraph 1
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	P24

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Rates, causes, place, and predictors of mortality in adults with intellectual disabilities with and without Down syndrome: cohort study with record linkage

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3 **Rates, causes, place, and predictors of mortality in**
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9 **Down syndrome: cohort study with record linkage**
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Abstract

Objectives

To investigate mortality in adults with intellectual disabilities: rates, causes, place, demographic and clinical predictors.

Design

Cohort study with record linkage to death data.

Setting

General community.

Participants

961/1,023 (94%) adults (16-83 years; mean=44.1 years; 54.6% male) with intellectual disabilities, clinically examined in 2001-2004; subsequently record-linked to their National Health Service number, allowing linkage to death certificate data, 2018.

Outcome measures

Standardised mortality ratios (SMRs), underlying, and all contributing causes of death, avoidable deaths, place, and demographic and clinical predictors of death.

Results

294/961 (30.6%) had died; 64/179 (35.8%) with Down syndrome, 230/783 (29.4%) without Down syndrome. SMR overall=2.24 (1.98, 2.49); Down syndrome adults=5.28 (3.98, 6.57), adults without Down syndrome=1.93 (1.68, 2.18); male=1.69 (1.42, 1.95), female=3.48 (2.90, 4.06). SMRs decreased as age increased. More severe intellectual disabilities increased SMR, but ability was not retained in the multivariable model. SMRs were higher for most ICD-10 chapters. For adults without Down syndrome, aspiration/reflux/choking, and respiratory infection were the commonest underlying causes of mortality; for Down syndrome adults "Down syndrome", and dementia were most common. Amenable deaths (29.8%) were double that in the general population (14%). 60.3% died in hospital. Mortality risk related to: percutaneous endoscopic gastrostomy/tube fed, Down syndrome, diabetes, lower respiratory tract infection at

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3 cohort-entry, smoking, epilepsy, hearing impairment, increasing number of prescribed
4 drugs, increasing age. Bowel incontinence reduced mortality risk.

7 **Conclusions**

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9 Adults with intellectual disabilities with and without Down syndrome have different SMRs
10 and causes of death which should be separately reported. Both die younger, from
11 different causes than other people. Some mortality risks are similar to other people, with
12 earlier mortality reflecting more multi-morbidity; amenable deaths are also common.
13 This should inform actions to reduce early mortality, e.g. training to avoid
14 aspiration/choking, pain identification to address problems before they are advanced,
15 and reasonable adjustments to improve health-care quality.
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26 **Strengths and limitations of this study**

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- 30 • Thorough methods of case ascertainment for intellectual disabilities at baseline.
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- 32 • Individual verification of intellectual disabilities and its severity, and detailed health
- 33 assessments at baseline.
- 34
- 35 • Longitudinal design.
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- 37 • Large cohort size and study duration, and successful record linkage for 94% of
- 38 participants.
- 39
- 40 • Limitations include that the study was conducted in only one part of Scotland, and
- 41 the reliance upon recorded cause of death from death certificates.
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Introduction

People with intellectual disabilities die at a younger age than other people; on average, 20 years younger,¹ or 28 years younger specifically for people with Down syndrome.² It has been demonstrated that people with intellectual disabilities receive poorer management of their long term conditions within primary health care services compared with the general population,³ and it is conceivable that this is one contributor to earlier mortality. It has been suggested that as many as 40% of deaths of people with intellectual disabilities may have been amenable to good quality health care.⁴⁻⁶ There has been a recent increase in research on mortality in people with intellectual disabilities, but very little research has distinguished people with intellectual disabilities with and without Down syndrome, or investigated the factors associated with risk of mortality, and causes of mortality.

Previous studies on death in people with intellectual disabilities had limitations such as small sample sizes, or non-representative populations. More recently, there have been large-scale studies which are more representative, having been drawn from intellectual disabilities registers, or social security or primary care data with record linkage to death certification. These have been undertaken in parts of Sweden, Australia, England, Finland, Canada, Ireland, and USA (supplementary table 1).⁵⁻¹⁹ These studies fairly consistently report standardised mortality ratios (SMRs) to be high for people with intellectual disabilities, more so at younger ages, and higher for women than men. Adult studies have tended to report SMRs in the region of 2-4, although in some, SMR is only slightly above 1.^{10,16,19} However, direct comparison between studies is not always possible, due to the different age ranges studied and methods of reporting.

- Supplementary table 1 -

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3 In view of the methods that studies have used for population identification (typically,
4 routine administrative data linked to death certifications), they provide little information
5 on the socio-clinical factors that influence SMR, or the risk factors associated with death,
6 beyond that of age and sex. Three studies reported SMR by level of intellectual
7 disabilities, with, broadly speaking, higher SMR with more severe intellectual
8 disabilities.^{7,10,17} Only three studies (different studies to those that reported on level of
9 intellectual disabilities) were able to report data separately for adults with intellectual
10 disabilities with and without Down syndrome; two found higher mortality rates for adults
11 with Down syndrome (SMR=7.6,⁹ and hazard ratio=9.21⁵) than for adults without Down
12 syndrome, or an odds ratio showing Down syndrome as a risk of death.¹² A further
13 study reported SMR=5.5 for children and adults (combined) with Down syndrome, but
14 did not report SMR for those with intellectual disabilities without Down syndrome.²⁰ Two
15 studies reported adults with intellectual disabilities to have higher SMRs if they have the
16 co-morbidities of epilepsy,^{5,7} and cerebral palsy,⁷ as opposed to not having these
17 comorbidities. One study reported adults with intellectual disabilities with comorbid
18 autism to have lower risk of mortality than those without comorbid autism.⁵ One study
19 reported the risk factors for mortality in a population with intellectual disabilities to be:
20 age, Down syndrome, cerebral palsy, blindness/low vision, technological
21 dependence/medical fragility, wheelchair dependence, mobility impairment without
22 wheelchair dependence, and epilepsy.¹² Factors not found to be risks, if any, were not
23 reported, and a further limitation was that factors were reported by agency staff, rather
24 than the individuals undergoing health assessments.¹² We have not identified any other
25 studies that investigated risk factors for time to mortality in adults with intellectual
26 disabilities.

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54 There is less consistency regarding the most common certified underlying causes of
55 death in adults with intellectual disabilities, partly as some studies do not report these
56 separately for children and adults, or by age ranges. Additionally, studies group causes
57 of death in different ways (e.g. pneumonia versus respiratory system), which can affect
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3 prevalence rankings between studies. Pneumonia, other respiratory diseases, and
4 diseases of the nervous system were reported to be the most common in one study,¹¹
5 diseases of the circulatory system and respiratory systems in another,⁵ heart disease,
6 neoplasm, and Alzheimer disease in a third,¹⁸ and diseases of the circulatory system,
7 neoplasm, and the nervous system in a fourth.¹⁹ In adults with intellectual disabilities,
8 cause specific SMRs have been reported to be high across most groups of disorders.^{5,11}
9 These studies did not report cause of death separately for adults with and without Down
10 syndrome. Given the different health profile of people with Down syndrome compared
11 with people with intellectual disabilities of other causes, this is an important limitation.²¹
12 In people with Down syndrome, most studies on mortality have been conducted with
13 child populations, and report the most common causes of death to be congenital heart
14 disease, and pneumonia/diseases of the respiratory system.²
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Overall, the existing body of literature on mortality in adults with intellectual disabilities does not include more detailed information on level of intellectual disabilities, nor separate out the population with, from those without, Down syndrome (for whom causes of death may differ), nor investigate health and demographic predictors of death other than age and sex, and is inconsistent with regards to causes of death. A better understanding of these factors may provide a pathway to action to reduce the observed earlier mortality in adults with intellectual disabilities.

This study aims to investigate the rates, causes, place, and demographic and clinical associations with mortality in adults with intellectual disabilities, with and without Down syndrome.

Methods

Approval

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3 Ethical approval was gained from NHS Greater Glasgow Primary Care Trust -
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5 Community & Mental Health Research Ethics Committee, and NHS Greater Glasgow and
6
7 Clyde Safe Haven. Individual consent to participate was taken in line with Scottish law,
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9 between 2001-2004.
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11 12 13 **Participants**

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15 The adult (aged 16+ years) intellectual disabilities population living within the NHS
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17 Greater Glasgow area was identified through multiple sources between 2000-2001.
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19 General practitioners were financially incentivised to identify their registered patients
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21 with intellectual disabilities, and all 631 (100%) did so. Adults were also identified via
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23 the intellectual disabilities health and social work services including day services, the
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25 Health Board register, and records of financial payments for any service by social work.
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27 This process led initially to an over-identification, such as people with IQ scores in the
28
29 70-80 range with additional complex health needs. All were systematically reviewed by
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31 nurses in the intellectual disabilities health service, and this group were removed. Thus,
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33 a register was compiled, and subsequently updated annually via general practices, with
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35 central support from the intellectual disabilities health service, until 2017 when services
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37 were redesigned. The identified adult prevalence of intellectual disabilities within the
38
39 area was 3.33 per 1,000 in 2000-2001.
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44 **Process and data collection**

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46 With initial piloting in 2001, each participant had a detailed assessment of their general
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48 and mental health, and demographic factors, completed 2002-2004. One of six specially
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50 trained, registered nurses reviewed each person's primary health care records, then
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52 used a semi-structured tool, the C21st Health Check, to assess clinical factors and the
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54 level and cause of intellectual disabilities. In addition to a review of existing health
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56 problems and all bodily health systems, a physical examination was undertaken,
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58 including assessment of vision and hearing, measurement of height and weight, and a
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60 phlebotomy protocol followed. All information was then reviewed by the nurse with one

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3 of three general practitioners with a special interest in intellectual disabilities, and any
4 further investigations that were indicated were completed. Previously known, and newly
5 identified, conditions were then classified using the *International Statistical Classification*
6 *of Diseases and Related Health Problems, 10th Revision (ICD-10)*.²² Anyone identified to
7 have possible, probable, or definite mental ill-health, autism, or problem behaviours was
8 then fully assessed by the project's intellectual disabilities psychiatrists. Each person's
9 assessment findings were then case conferenced by the two Consultant psychiatrists,
10 and diagnoses were derived and agreed according to clinical diagnoses, *ICD-10*
11 *(Diagnostic Criteria for Research)*,²³ *Diagnostic and Statistical Manual of Mental*
12 *Disorders-IV-TR*,²⁴ and *Diagnostic Criteria for Psychiatric Disorders for use with Adults*
13 *with Learning Disabilities (DC-LD)*.²⁵ Information was also collected on demographics,
14 and community, hospital, and social service use. Further details are provided
15 elsewhere.^{26,27} The data were entered into a database by two dedicated data-entry staff.

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31 Each person in Scotland is given a number unique to them at birth or first registration
32 with a general practitioner, which is used in almost all subsequent health service
33 encounters, and on certification of death. The numbers are held on the Community
34 Health Index (CHI) database at National Services Scotland. These CHI numbers provided
35 a means to record link each participant with National Records for Scotland death
36 certification data. This linkage was performed in 2018, and the linked data were held in
37 the NHS Greater Glasgow & Clyde (NHS GG&C) Safe Haven. Data on immediate,
38 underlying, and contributory causes of deaths by ICD-10 codes, age at death, and place
39 of death were extracted.

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51 In order to provide finer granularity of cause of death, two clinical academics then
52 grouped specific causes of death into narrower groupings than those provided by ICD-10
53 chapter headings (supplementary table 2). This approach was also in view of the
54 recognised issue of variation between health staff in distinguishing and recording
55 immediate causes of death, and because some causes occurred in low numbers so could

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3 not be individually reported due to the risk of statistical disclosure. Additionally, some
4 conditions likely to be the same are spilt between different ICD-10 chapters, e.g.
5 dementia in Alzheimer disease (F00) and unspecified dementia (F03) in the ICD-10
6 mental and behavioural disorders chapter, and Alzheimer's disease (G30) and
7 Alzheimer's disease, unspecified (G30.9) in the ICD-10 diseases of the nervous system
8 chapter. A list of related conditions was generated by one of the clinical academics and
9 then checked by the second.
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19 - Supplementary table 2 -
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23 **Analyses**

24 All statistical analyses were conducted using R for Windows v3.3.0 or SAS 9.3 (SAS
25 Institute, Cary NC) and were performed within the NHS GG&C Safe Haven environment.
26 Due to disclosure principles of the Safe Haven, results with counts of less than 5 cannot
27 be released; these have been referred to as <5 throughout. Similarly, if it is deemed
28 possible that participants may be identified from the results, these may be omitted.
29 Details are provided if this occurred.
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40 Data were summarised for the population of adults aged 16+ years with intellectual
41 disabilities. Categorical variables were summarised with the number and percentages of
42 people falling into each category and the number of missing data. Continuous variables
43 were summarised with the number of observations and those missing, the mean and
44 standard deviation (SD), and the minimum and maximum values, unless otherwise
45 stated.
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54 Participant characteristics were summarised overall and for those alive and those
55 deceased. For those who are deceased, their data including age at death,
56 underlying/contributing causes of death, and location of death were summarised for
57 those with and without Down syndrome. Location codes for place of death are provided
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3 where available. We assumed those with the code for non-institutional location to have
4 died at home. Due to small numbers, location codes have been grouped together for
5 NHS hospitals, home, and other hospitals/care facilities including hospices.
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11 Mortality incidence rates have been calculated using the number of deaths in the cohort
12 divided by the number of person years alive within the study period multiplied by
13 100,000, overall and for those with and without Down syndrome. SMRs were calculated
14 using population data for those aged 15 and over within NHS GG&C in 2010.^{28,29} Death
15 rates for males and females by 5 year band ages groups spanning from 15-20 years old
16 to 90 years and over were summed to form the expected death rates for the general
17 population. The observed death rate for adults with intellectual disabilities was taken
18 from our study results. The observed/expected death rates were calculated for the
19 intellectual disabilities cohort overall then separately by age group, sex, ability level, and
20 for the adults with, and without, Down syndrome, and ICD-10 chapter for cause of
21 death, and compared to the general population.
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36 Deaths were also analysed for those that could be considered as deaths that would have
37 been avoidable. The Office for National Statistics (ONS) published a definition of
38 avoidable mortality,³⁰ which lists the causes of amenable deaths (deaths that should not
39 occur in the presence of good health care, e.g. respiratory disease), and causes of
40 preventable deaths (e.g. from diseases that could have been avoided by prior
41 immunisation), by ICD-10 codes. Causes of death for the adults with intellectual
42 disabilities have been summarised by ONS definition of avoidable deaths.
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51 To determine the demographic and clinical factors associated with death in adults with
52 intellectual disabilities, time to event analyses were explored using univariate Cox
53 Proportional Hazards models. Variables were selected as potentially relevant on the basis
54 of what is known on causes of death in people with intellectual disabilities, the 20 most
55 common physical health conditions reported in the adult population with intellectual
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3 disabilities,²¹ and other factors hypothesised as potentially clinically relevant

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5 (supplementary table 3):

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- Demographics - 9 variables.
 - Clinical conditions - 33 variables.
 - Service use - 3 variables.
 - Prescriptions - 5 variables.
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15 All 50 variables were then permitted entry in to a single multivariable analysis using
16 stepwise regression methods, in order to identify a model containing the statistically
17 significant factors associated with death. Age at date of the health assessment was
18 entered in to the model as a continuous measure. Results from the univariate Cox
19 Proportional Hazards models (Supplementary table 3) and the statistically significant
20 multivariable model from the stepwise results have been presented with hazard ratios
21 with corresponding 95% confidence intervals (HR, 95% CI) and p-values were obtained.
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31 - Supplementary table 3 -
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34 35 ***Patient and public involvement***

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37 This study was designed to respond to the growing concern expressed by people with
38 intellectual disabilities, their families, and third sector organisations about the early
39 deaths of people with intellectual disabilities. The Scottish Learning Disabilities
40 Observatory, where this research was undertaken, has a specific remit for people with
41 intellectual disabilities. Its steering group includes partners from third sector
42 organisations, including Down syndrome Scotland, and people with intellectual
43 disabilities, who approved the work plan for this project prior to it commencing. Results
44 from this study will be disseminated for people with intellectual disabilities in an easy-
45 read version via the Scottish Learning Disabilities Observatory.
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58 **Results**

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Population characteristics

962 of the original 1,023 (94.0%) adults with intellectual disabilities who were assessed were linked to a CHI number enabling the extraction of relevant death data. Reasons for the unlinked 61 people could be due to moving out of the area, or a recording mistake. 1 further participant was removed from the analysis due to inaccurate recording of dates, leaving 961 adults in the cohort (93.9%). Of these 961 adults, 294 (30.6%) had a record of death. Table 1 shows the baseline characteristics of the full cohort of 961, the adults who died, and those still alive at the time of linkage.

- Insert table 1 about here -

Age at death, and mortality incidence

The mean age at death was 61.0 years (SD=7.0 years). Of the 961 adults, 64 (35.8%) of the 179 adults with Down syndrome, and 230 (29.4%) of the 782 adults without Down syndrome had a record of death. Their mean age of death was 56.9 years (SD=4.3 years) for the adults with Down syndrome, and 62.2 years (SD=7.5 years) for the adults without Down syndrome. Mortality incidence for the cohort during the study period was 3,049.0 per 100,000 person years follow-up, with 3,832.1 per 100,000 for those with Down Syndrome and 2,885.0 for those without Down syndrome.

Standardised mortality ratios

Compared with the general population, the SMR was 2.24 (1.98, 2.49) overall; 5.28 (3.98, 6.57) for adults with Down syndrome, 1.93 (1.68, 2.18) for adults without Down syndrome; 1.69 (1.42, 1.95) for men and 3.48 (2.90, 4.06) for women. SMRs were higher the more severe the level of intellectual disabilities, with people with profound intellectual disabilities having an SMR of 4.14 (3.11, 5.17). SMR was high for all age groups (though for the 15-25 year age group, the wide confidence interval includes one, perhaps due to the smaller number of deaths in this group); this decreased as age increased. SMRs were high for most ICD-10 chapter groups of conditions, particularly so

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3 for congenital malformations at 17.26 (10.75, 23.78), diseases of the digestive system
4 at 16.13 (8.23, 24.04), mental and behavioural disorders at 12.64 (3.27, 22.00), and
5 external causes at 11.08 (3.40, 18.76). Details are shown in table 2.
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11 - Insert table 2 about here -
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14 15 **Causes of death**

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17 Cause of death data was available from death certificates for 262 (89.1%) of 294
18 participants who had died, which include 57 (89.1%) participants with Down syndrome,
19 and 205 (88.7%) participants without Down syndrome. Table 3 shows the underlying
20 causes of death by ICD-10 chapters separately for the adults with, and without Down
21 syndrome. For the whole cohort, diseases of the respiratory system were the most
22 common (21.8%), then diseases of the circulatory system (19.1%), then diseases of the
23 nervous system (13.0%), and neoplasms, followed by congenital anomalies (10.3%).
24 For the adults with Down syndrome, congenital anomalies were the most common (in all
25 cases this was a record of "Down syndrome"), then jointly diseases of the respiratory
26 system and diseases of the circulatory system, then diseases of the nervous system,
27 followed by infections, and mental and behavioural disorders. For the adults without
28 Down syndrome, diseases of the respiratory system were the most common, then
29 diseases of the circulatory system, then neoplasms, then diseases of the nervous
30 system, followed by diseases of the digestive system. Table 4 presents the most
31 common underlying causes of death by individual causes, or related groups of causes,
32 with finer granularity than ICD-10 chapter headings (groups are shown in supplementary
33 table 2). Causes are listed in the order of how common they were in the whole cohort.
34 Data are presented separately for the adults with, and without Down syndrome. For the
35 whole cohort, the most common cause was aspiration/reflux/choking, then respiratory
36 infection, then other malignancy (non gastrointestinal), then other condition (mostly
37 unrelated conditions that could not be reported individually or as groups, due to
38 individually occurring at a frequency of <5). For the adults with Down syndrome, Down
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3 syndrome was the most common cause, then dementia, then other infection. For the
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5 adults without Down syndrome, aspiration/reflux/choking was the most common cause,
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7 then respiratory infection, then other malignancy (non gastrointestinal). For the 21
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9 people whose death certificate listed Down syndrome as their underlying cause of death,
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11 the death certificates were reviewed and underlying cause of death reclassified, as a
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13 sensitivity check. Following this, the most common underlying causes of death for the
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15 adults with Down syndrome were dementia (n=20; 35.1%), then other infection (n=7;
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17 12.3%).
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21 - Insert tables 3 and 4 about here -
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25 Table 5 shows the all contributing causes of death data, again presenting the most
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27 common causes by individual causes, or related groups of causes with finer granularity
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29 than ICD-10 chapter headings. Data is presented separately for the adults with, and
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31 without Down syndrome. For the whole cohort, respiratory infection was the most
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33 common cause (27.1%), followed by aspiration/reflux/choking (19.8%), other conditions
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35 (15.6%), other cardiovascular conditions (non acute myocardial nor other ischaemic
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37 heart disease: 14.5%), then other respiratory conditions. For the adults with Down
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39 syndrome, Down syndrome was the most common, then dementia, then respiratory
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41 infection, then aspiration/reflux/choking. For the adults without Down syndrome,
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43 respiratory infection was the most common cause, then aspiration/reflux/choking, then
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45 other condition, then other respiratory conditions, and intellectual disabilities.
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49 - Insert table 5 about here -
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52 53 **Avoidable deaths**

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55 According to the ONS list of avoidable deaths, 102 (38.9%) of the 262 deaths were
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57 avoidable; most notably, respiratory infection and epilepsies (table 4). 78 (29.8%) were
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59 deaths that are amenable to good health care, whilst 51 (19.5%) were preventable
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3 deaths. 27 (10.3%) deaths were classed as both amenable and preventable deaths. This
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5 compares to published Scottish death data showing in 2018 that 28% of deaths were
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7 avoidable; 14% amenable and 24% preventable, similar to the figures in the previous
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9 four years (data not available prior to 2014).³¹ For the 57 deaths of adults with Down
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11 syndrome, 17 (29.8%) deaths were avoidable, 15 (26.3%) deaths were amenable to
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13 good health care, whilst 7 (12.3%) were preventable. 5 (8.8%) were both amenable and
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15 preventable. For the 205 deaths of adults without Down syndrome, 85 (41.5%) were
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17 avoidable, 63 (30.7%) deaths were amenable to good health care, whilst 44 (21.5%)
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19 were preventable. 22 (10.7%) were both amenable and preventable.
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23 ***Place of death***

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25 Of the 262 participants for whom place of death was known, 158 (60.3%) died in an
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27 NHS Hospital, 70 (26.7%) died at home, and 34 (13.0%) died within other
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29 hospitals/care facilities. This was similar for both the adults with Down syndrome: 31
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31 (54.4%) in an NHS hospital, 17 (29.8%) at home, and 9 (15.8%) within other
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33 hospitals/care facilities; and the adults without Down syndrome: 127 (62.0%) in an NHS
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35 hospital, 53 (25.9%) at home, and 25 (12.2%) within other hospitals/care facilities.
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39 ***Factors associated with risk of death***

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41 The results from the univariate cox proportional hazards models indicated that of the
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43 original 50 potential variables, factors associated with risk of death were (supplementary
44
45 table 3):
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- 47 • Demographics – age at the time of the health assessment, more severe learning
48 disabilities, accommodation type (not living with family carer), not having day-time
49 occupation, and being a smoker (but not sex, the extent of neighbourhood
50 deprivation, civil status, nor Down syndrome, in view of the confidence intervals).
- 51 • Clinical conditions – having spastic quadriplegia, hearing impairment, visual
52 impairment, diabetes, percutaneous endoscopic gastrostomy/tube fed, constipation,
53 ataxia/gait disorder, osteoporosis, hypertension, dysphagia, dyspnoea, gastro-
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oesophageal reflux disorder, lower respiratory tract infection, total number of physical health disorders, not having impaired mobility, not having urinary incontinence, not having bowel incontinence, and not having autism (but not epilepsy, body mass index, nail disorder, epidermal thickening, cerebral palsy, fungal infection, musculoskeletal pain, bone deformity, dental/oral problem, eczema/dermatitis, psychosis, affective disorder including bipolar affective disorder, problem behaviour, eating disorder including pica, nor any mental illness).

- Service use – number of general practitioner consultations in the previous 12 months, total number of different types of health professionals providing care at the time of the clinical assessment, (but not number of accident and emergency attendances in the previous 12 months).
- Prescriptions – antiepileptic drugs, total number of different types of drugs, (but not antipsychotic drugs, antidepressant drugs, nor anxiolytic drugs).

Table 6 shows the final model of the variables retained in the multivariable analysis for time to death. The significant factors indicating an increased risk of death were increased age at the time of the health assessment, smoking, Down syndrome, diabetes, being percutaneous endoscopic gastrostomy/tube fed, lower respiratory tract infection at cohort inception, epilepsy, hearing impairment, and total number of different types of drugs prescribed, whilst bowel incontinence showed a reduced risk of death. Of note, level of intellectual disabilities whilst significant in the univariate analysis, was not retained in the multivariable model.

- Insert table 6 about here -

Discussion

Principle findings and interpretation

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3 As far as we are aware, this is the first population-based study of adults with intellectual
4 disabilities to report in detail the factors associated with time to death, and to describe
5 their causes of death and quantify the SMR separately for adults with Down syndrome
6 and adults without Down syndrome. This is important, since adults with Down syndrome
7 form a notable proportion of all adults with intellectual disabilities (19% in this cohort),
8 and because they have a different pattern of clinical conditions compared with other
9 adults with intellectual disabilities.²¹ We found that aspiration/reflux/choking is the most
10 common underlying cause of death in adults with intellectual disabilities, followed by
11 respiratory infection. They are also the most common all contributing causes of death.
12 The profile differed in the adults with Down syndrome for whom "Down syndrome",
13 followed by dementia, were recorded as the most common underlying cause of death,
14 and all contributing causes of death (or alternatively, dementia, then other infection
15 were the most common underlying causes when "Down syndrome" deaths were
16 reclassified); with the next most common all contributing cause of death being
17 respiratory infection, then aspiration/reflux/choking. The proportion of deaths that would
18 have been amenable to good care for adults with intellectual disabilities was more than
19 double that seen in the general population. Although aspiration/reflux/choking is not
20 included in the ONS list of avoidable deaths, and therefore not included in the figures we
21 report on amenable deaths, we consider that good care could have prevented many of
22 these deaths. This appears to be very important for adults with intellectual disabilities
23 irrespective of whether they have Down syndrome. Similarly, some other causes of
24 deaths within this cohort (supplementary table 2), such as constipation/mega-colon, and
25 urinary tract infections do not appear on the ONS list of avoidable deaths.

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52 Clearly, this pattern of causes of death differs from that seen in the general population,
53 in whom the most common underlying causes of death are heart disease, then dementia,
54 then lung cancer in men, and dementia, then heart disease, then stroke in women.³²
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Clearly, this pattern of causes of death differs from that seen in the general population, in whom the most common underlying causes of death are heart disease, then dementia, then lung cancer in men, and dementia, then heart disease, then stroke in women.³² When all cancers are grouped together, in the general population, cancer is the leading underlying cause of death in 30% of men and 26% of women, compared with this study

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3 reporting 0% for adults with Down syndrome, and 15.2% for adults with intellectual
4 disabilities without Down syndrome – presumably as the adults with intellectual
5 disabilities are dying younger from other causes, and cancers increase with age.
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11 We found an overall SMR of 2.24; 5.28 in the adults with Down syndrome and 1.93 for
12 the adults without Down syndrome. SMRs were higher for most ICD-10 chapter
13 groupings of conditions. It was higher in the women than the men, as has been
14 previously reported in most (supplementary table 1), but not all^{10,19} previous reports.
15 The reason for this is unknown; in the general population, mortality rates have fallen in
16 recent decades, and more so in middle and older aged men than women (i.e. the sex
17 gap is narrowing at these ages), but we do not know what trends over time there have
18 been for people with intellectual disabilities. Having intellectual disabilities removes
19 differences in lifespan by sex compared with the general population; but sex was not a
20 predictor of mortality in our study, so the SMR difference may only be because of the
21 difference found in the general population by sex. SMRs were lowest with older age
22 groups, likely to be due to increased illness in the older general population and
23 conversely a healthier group with intellectual disabilities living to older ages compared
24 with those who die younger. Although SMR was higher with increasing severity of
25 intellectual disabilities, ability level was not retained within the multivariable model on
26 time to death. The factors that were independently associated with increased risk of
27 death, in order, were being percutaneous endoscopic gastrostomy/tube fed, Down
28 syndrome, diabetes, having a lower respiratory tract infection at entry to the cohort,
29 smoking, epilepsy, hearing impairment, total number of prescribed drugs, and age,
30 whilst bowel incontinence had a reduced risk of death. Some of these predictors are
31 similar to those reported in the general population, suggesting earlier mortality of adults
32 with intellectual disabilities is largely accounted for by the higher rates of multi-
33 morbidities that they experience compared with other people, and amenable deaths.³³
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3 Whilst accommodation type (not living with a family carer), ability level, not having day-
4 time occupation, having spastic quadriplegia, visual impairment, constipation, ataxia/gait
5 disorder, osteoporosis, hypertension, dysphagia, dyspnoea, gastro-oesophageal reflux
6 disorder, total number of physical health disorders, not having impaired mobility, not
7 having urinary incontinence, and not having autism, number of general practitioner
8 consultations in the previous 12 months, total number of different types of health
9 professionals providing care at the time of the health assessment, and antiepileptic
10 drugs were related to time of death on univariate analyses, they were not retained in the
11 multivariable model.
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23 The majority of the adults with intellectual disabilities, with and without Down syndrome,
24 died in an NHS hospital.
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29 ***Comparison with previous literature***

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31 The overall SMR we report, higher SMR in women than men, and higher SMR at younger
32 age groups is similar to the majority of previous reports. Most mortality studies with
33 people with Down syndrome have been conducted with children. Previous reports of
34 children and adults (combined) gave an SMR=5.5,²⁰ and for adults SMR=7.6,⁹ compared
35 with our finding for adults with Down syndrome of SMR=5.28. Recent systematic reviews
36 reported people with intellectual disabilities on average died 20 years younger than other
37 people, and people with Down syndrome died 28 years younger, although the majority
38 of the Down syndrome studies were not recent.^{1,2} In our study we found the gap
39 between the age at death of people with intellectual disabilities with and without Down
40 syndrome to be only 5.3 years, possibly reflecting the increasing lifespan of people with
41 Down syndrome exceeding increases in lifespan for people with intellectual disabilities
42 without Down syndrome. Notably, after "Down syndrome", dementia was the most
43 commonly reported underlying, and all contributing cause of death for the adults with
44 Down syndrome, whereas studies in the past commented on congenital heart disease
45 and respiratory causes.
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5 For the cohort overall, respiratory infection and aspiration/reflux/choking were the most
6 common all contributing causes of death. These conditions feature in previous studies on
7 causes of death,^{5,6,8,10,11} although there are inconsistencies between studies. By ICD-10
8 chapter, our study found the most common underlying causes of death were diseases of
9 the respiratory system, then of the circulatory system, followed by neoplasms. Others
10 reported the most common to be vascular,¹⁰ circulatory,⁵ heart disease,¹⁷ and jointly
11 circulatory and neoplasm.¹⁹
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22 Previous research from other countries has highlighted that listing Down syndrome or
23 intellectual disabilities as the underlying cause of death obscures actual causes of death for
24 this population.³⁴ We therefore presented data on revised cause of death for the 21 people
25 for whom it was listed as Down syndrome (as a sensitivity check), and highlight with interest
26 that in this Scottish cohort no-one had intellectual disabilities listed as underlying cause of
27 death. This may reflect different medical death certificate recording practices in Scotland
28 compared to e.g. USA.
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41 Studies that investigated avoidable deaths in adults with intellectual disabilities found
42 them to be more common than in the general population, due to deaths that would have
43 been amenable to good care. Avoidable deaths have been reported in 44.7% of deaths
44 of people with intellectual disabilities in England (mostly amenable deaths – figure not
45 reported),⁶ and in 31% in Australia,¹⁹ compared with our figure of 38.9%. Avoidable
46 deaths that would have been amenable to good care have been reported to occur in 37%
47 of deaths of people with intellectual disabilities in England.⁵ Our figure is slightly lower at
48 29.8% but still more than double that found in the Scottish general population.³¹ It
49 should be noted that the ONS list of avoidable deaths was not designed specifically for
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3 people with intellectual disabilities, and it may emphasise some causes less relevant, and
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5 omit others that might be highly relevant in this population.⁵
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9 ***Strengths and limitations***

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11 The strengths of the study include the thorough methods of case ascertainment for
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13 intellectual disabilities at baseline with verification of intellectual disabilities and its
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15 severity, suggesting results are generalisable in other high income countries. Whilst our
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17 Identification of the population will not have identified everyone with intellectual
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19 impairment (an IQ<70), in view of the multiple sources used, we believe it will have
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21 identified the adults with intellectual disabilities (IQ<70, plus need for support in daily
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23 activities, and onset in the developmental period). Additionally, there were detailed
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25 clinical assessments at baseline, and a longitudinal design. The size of the cohort and the
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27 duration of follow-up is also a strength, as is the successful record linkage for 94% of
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29 participants. Our study does have limitations, specifically that the study was only
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31 conducted in one region of Scotland, and the reliance upon death certificate data to
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33 obtain cause of death. Additionally, the characteristics and health of the participants was
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35 collected in 2002-2004. The health conditions we investigated tend to be long-standing
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37 or remitting/relapsing conditions, and psychotropic prescribing also once initiated tends
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39 to be long-standing in people with intellectual disabilities. However, it is possible that
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41 extent of neighbourhood deprivation, type of accommodation, employment, and civil
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43 status (though few marry) might have changed for some people between 2002-2004 and
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45 2018; we have no further information to check this. There were no concerns regarding
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47 the proportional hazards assumption in the multivariable model. The linkage was also
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49 reliant on the accuracy of the CHI number as a sole source of linkage.
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54 ***Implications***

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56 It is important to know the factors that are associated with risk of death, and the
57
58 common causes of death in this population, as these then inform the actions needed to
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60 reduce the unacceptably high SMRs experienced by people with intellectual disabilities.

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3 Awareness of these factors may provide a pathway to action to reduce the observed
4 earlier mortality in adults with intellectual disabilities. It is not adequate to solely rely on
5 the public health interventions available to everyone, even when they are accessible.
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7 Aspiration, reflux, and choking could, and should, be avoided by raising awareness of its
8 consequences (death), and putting in place training on simple measures related to
9 feeding, positioning, food consistency, and when to seek health advice from speech and
10 language therapy, physiotherapy, nursing, and medical advice. Carers need to be aware
11 of how the adults they care for express pain, so that conditions such as gastrointestinal
12 ulcers are attended to, prior to the extreme point of perforation, and so treatable
13 conditions such as constipation and urinary tract infections are managed before they
14 lead to respiratory distress and sepsis. Quality of care is important; adults with
15 intellectual disabilities need just as good care for their diabetes and epilepsy (and other
16 conditions) as the rest of the population, with reasonable adjustments to address
17 accessibility, and accessible smoking cessation programs.
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33 **Future research**

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35 Further research on larger samples is needed, particularly with regards to replicating and
36 extending our findings on the factors that are associated with risk of death, and any sex
37 differences in them, so that practitioners can focus on actions to improve the life
38 expectancy of adults with intellectual disabilities, with and without Down syndrome.
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42 submit the article for publication.
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46 The researchers are independent from the funders.
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50 **Competing interests**

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54 The authors declare no competing interests.
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58 **Author's contributions**

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5 S-AC is principle investigator, she conceived and managed the project, interpreted data,
6
7 and wrote the first draft of the manuscript. LA contributed to the conception of the
8
9 project, and project management. NG designed and supervised the statistical analysis,
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11 and contributed to data interpretation and drafting of the manuscript. PMcS implemented
12
13 and refined the statistical analysis, and contributed to data interpretation, and drafting of
14
15 the manuscript. AJ implemented and refined the statistical analysis, and contributed to
16
17 data interpretation. AH contributed to data linkage and interpretation, and drafting of the
18
19 manuscript. CMcC provided expertise on data linkage and methods, and drafting of the
20
21 manuscript. DK contributed to data interpretation and drafting of the manuscript. CM
22
23 contributed to data interpretation, and drafting of the manuscript. All approved the final
24
25 version of the manuscript. S-AC is the study guarantor.
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29 **Data sharing**

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34 Data is available via NHS GG&C Safe Haven upon application.
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38 **Acknowledgments**

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46 and their carers.
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Table 1. Cohort characteristics at time of the health assessment, summarised overall and by death status during the follow-up period

Variable	Statistics / Groups	All participants (N=961)	Deceased participants (N=294)	Alive participants (N=667)
Age (years)	Mean (SD)	44.1 (14.6)	52.4 (13.6)	40.5 (13.6)
	Min, max	16, 83	18, 83	16, 77
Age group	16-25 years	127 (13.2%)	10 (3.4%)	117 (17.5%)
	26-35 years	153 (15.9%)	26 (8.8%)	127 (19.0%)
	36-45 years	246 (25.6%)	49 (16.7%)	197 (29.5)
	46-55 years	205 (21.3%)	85 (28.8%)	120 (18.0%)
	>55 years	230 (23.9%)	124 (42.0%)	106 (15.9%)
Sex	Male	525 (54.6%)	154 (52.4%)	371 (55.6%)
	Female	436 (45.3%)	140 (47.5%)	296 (44.4%)
Ability level	Mild ID	382 (39.7%)	92 (31.2%)	290 (43.5%)
	Moderate ID	236 (24.5%)	73 (24.7%)	163 (24.4%)
	Severe ID	180 (18.7%)	67 (22.7%)	113 (16.9%)
	Profound ID	163 (17.0%)	62 (21.1%)	101 (15.1%)
Accommodation type	Family carer	374 (38.9%)	70 (23.8%)	304 (45.6%)
	Independent	93 (9.7%)	36 (12.2%)	57 (8.5%)
	Paid support	435 (45.2%)	161 (54.6%)	274 (41.1%)
	Congregate care	59 (6.1%)	27 (9.2%)	32 (4.8%)
Down syndrome	No	782 (81.4%)	230 (78.2%)	552 (82.8%)
	Yes	179 (18.6%)	64 (21.7%)	115 (17.2%)

ID=intellectual disabilities; SD=standard deviation

Table 2. Standardised mortality ratios

Variable	Groups	SMR (95% CI)
All participants	-	2.24 (1.99, 2.50)
Age group*	15-25 years	18.73 (0.37, 37.09)
	26-35 years	4.21 (1.29, 7.13)
	36-45 years	3.86 (2.28, 5.44)
	46-55 years	3.77 (2.90, 4.74)
	>55 years	1.86 (1.60, 2.12)
Sex	Male	1.69 (1.42, 1.95)
	Female	3.48 (2.90, 4.06)
Ability level	Mild ID	1.60 (1.27, 1.92)
	Moderate ID	2.10 (1.62, 2.58)
	Severe ID	2.78 (2.11, 3.44)
	Profound ID	4.14 (3.11, 5.17)
Down syndrome	No	1.93 (1.68, 2.18)
	Yes	5.28 (3.98, 6.57)
Underlying causes of death grouped by ICD-10 chapter**	Congenital malformations, deformations and chromosomal abnormalities	17.26 (10.75, 23.78)
	Diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism	7.50 (-7.20, 22.20)
	Diseases of the circulatory system	5.55 (4.01, 7.09)
	Diseases of the digestive system	16.13 (8.23, 24.04)
	Diseases of the genitourinary system	3.65 (0.73, 6.57)
	Diseases of the musculoskeletal system and connective tissue	5.40 (-0.71, 11.52)
	Diseases of the nervous system	7.73 (5.13, 10.32)
	Diseases of the respiratory system	6.78 (5.02, 8.54)

	Diseases of the skin and subcutaneous tissue	2.75 (-2.64, 8.15)
	Endocrine, nutritional and metabolic diseases	3.43 (1.05, 5.81)
	External causes of morbidity and mobility	11.08 (3.40, 18.76)
	Infectious and parasitic diseases	8.93 (1.78, 16.07)
	Mental and behavioural disorders	12.64 (3.27, 22.00)
	Neoplasms	6.31 (4.19, 8.43)
	Symptoms, signs and abnormal clinical and laboratory findings, not elsewhere classified	19.51 (0.39, 38.63)

CI=confidence intervals; ID=intellectual disabilities; SMR=standardised mortality ratios

*Data used for comparison with General Population (GG&C Health Board) provides data in 5 year age bands therefore 15+. Data on adults with ID are 16+

** Negative Lower CI and wide CIs indicate low number of observed deaths in study population

Table 3. Underlying causes of death grouped by ICD-10 chapter, where cause of death is known

ICD-10 chapter	Participants with Down syndrome (N=57)	Participants without Down syndrome (N=205)
Certain infectious and parasitic diseases	5 (8.8%)	<5
Neoplasms	<5	33 (16.1%)
Diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism	<5	<5
Endocrine, nutritional and metabolic diseases	<5	8 (3.9%)
Mental and behavioural disorders	5 (8.8%)	<5
Diseases of the nervous system	7 (12.3%)	27 (13.2%)
Diseases of the eye and adnexa	<5	<5
Diseases of the ear and mastoid process	<5	<5
Diseases of the circulatory system	8 (14.0%)	42 (20.5%)
Diseases of the respiratory system	8 (14.0%)	49 (23.9%)
Diseases of the digestive system	<5	16 (7.8%)
Diseases of the skin and subcutaneous tissue	<5	<5
Diseases of the musculoskeletal system and connective tissue	<5	<5
Diseases of the genitourinary system	<5	5 (2.4%)
Pregnancy, childbirth and the puerperium	<5	<5
Certain conditions originating in the perinatal period	<5	<5
Congenital malformations, deformations and chromosomal abnormalities	21 (36.8%)	6 (2.9%)
Symptoms, signs and abnormal clinical and laboratory findings, not elsewhere classified	<5	<5
External causes of morbidity and mortality	<5	7 (3.4%)
All deaths	57 (100%)	205 (100%)

ICD-10=International Statistical Classification of Diseases and Related Health Problems, 10th Revision

Table 4. Underlying causes of death grouped by specific individual causes or related groups of causes, where cause of death is known

Causes	Participants with Down syndrome (N=57)	Participants without Down syndrome (N=205)
Aspiration/reflux/choking	<5	22 (10.8%)
Respiratory infection	<5	21 (10.3%)
Down syndrome	21 (36.8%)	<5
Other malignancy	<5	19 (9.3%)
Other condition	<5	17 (8.3%)
Epilepsies	<5	13 (6.4%)
Acute myocardial infarction	<5	13 (6.4%)
Gastro-intestinal malignancy	<5	12 (5.9%)
Stroke	<5	11 (5.4%)
Other cardiovascular disease	<5	11 (5.4%)
Other respiratory condition	<5	9 (4.4%)
Other infection	5 (8.8%)	6 (2.9%)
Cerebral palsy	<5	11 (5.4%)
Dementia	9 (15.8%)	<5
Other gastrointestinal disorders	<5	8 (3.9%)
Ulcer/gastrointestinal perforation	<5	7 (3.4%)
Diabetes	<5	7 (3.4%)
Other congenital condition	<5	6 (2.9%)
Other ischaemic heart condition	<5	6 (2.9)
Mental health	<5	<5
Other neurological conditions	<5	<5
Renal failure	<5	<5
All deaths	57 (100%)	205 (100%)

Table 5. All contributing causes of death grouped by specific individual causes or related groups of causes, where cause of death is known

Causes	Participants with Down syndrome (N=57)	Participants without Down syndrome (N=205)
Respiratory infection	22 (38.6%)	49 (23.9%)
Aspiration/reflux/choking	11 (19.3%)	41 (20.0%)
Down syndrome	43 (75.4%)	<5
Other condition	8 (14.0%)	33 (16.1%)
Other cardiovascular disease	8 (14.0%)	30 (14.6%)
Other respiratory conditions	<5	31 (15.1%)
Other infection	9 (15.8%)	24 (11.7%)
Intellectual disabilities	<5	31 (15.1%)
Epilepsies	8 (14.0%)	24 (11.7%)
Dementia	24 (42.1%)	<5
Other neoplasms	<5	23 (11.2%)
Cerebral palsy	<5	24 (11.7%)
Acute myocardial infarction	5 (8.8%)	19 (9.3%)
Other gastrointestinal disorders	<5	18 (8.8%)
Diabetes	<5	19 (9.3%)
Other ischaemic heart disease	<5	19 (9.3%)
Renal failure	<5	16 (7.8%)
Stroke	<5	17 (8.3%)
Other congenital condition	<5	15 (7.3%)
Gastrointestinal malignant neoplasm	<5	12 (5.9%)
Ulcer/gastrointestinal perforation	<5	10 (4.9%)
Mental health	<5	10 (4.9%)
Other neurological condition	<5	8 (3.9%)
Heart failure	<5	7 (3.4%)
Injuries and accidents	<5	8 (3.9%)
Medical/surgical complications	<5	<5
Secondary malignancies	<5	<5
Thyroid disorders	<5	<5
Metabolic disorder	<5	<5
All deaths	57 (100%)	205 (100%)

Table 6. Multivariable model results for the outcome time to death

Variable		Hazard ratio	95% CI	p-value
Age at time of health assessment		1.056	1.046, 1.066	<0.0001
Smoker	No	1	-	
	Yes	1.531	1.1011, 2.128	0.0112
Down syndrome	No	1	-	
	Yes	2.440	1.787, 3.332	<0.0001
Epilepsy	No	1	-	
	Yes	1.511	1.173, 1.946	0.0014
Hearing impairment	No	1	-	
	Yes	1.320	1.030, 1.692	0.0284
Bowel incontinence	No	1	-	
	Yes	0.490	0.376, 0.640	<0.0001
Diabetes	No	1	-	
	Yes	2.346	1.553, 3.542	<0.0001
PEG/tube fed	No	1	-	
	Yes	2.346	1.135, 5.989	0.00240
Lower respiratory track infection	No	1	-	
	Yes	1.782	1.315, 2.415	0.0002
Total number of prescribed drugs		1.066	1.016, 1.118	0.0085

CI=confidence interval; PEG=percutaneous endoscopic gastrostomy

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Supplementary table 1. Previously reported standardised mortality ratios, causes, and risks for death

Author	Country	SMR (95% confidence interval)	Number of deaths	Causes of death and risk factors for death
Forsgren et al (1996) ⁷	Sweden	4.2 (3.3, 5.3) at 20-59y; 1.1 (0.9, 1.5) at 60+y <i>Without epilepsy:</i> 3.8 (2.8, 5.0) at 20-59y; 1.1 (0.8, 1.5) at 60+y <i>With epilepsy:</i> 5.0 (2.9, 8.7) at 20-59y; 2.4 (0.9, 6.1) at 60+y <i>With epilepsy and cerebral palsy:</i> 8.0 (4.1, 15.7) at 20-59y; 0.9 (0.1, 6.6) at 60+y <i>M:</i> 1.6 (1.2, 2.0) at 0-60+y <i>F:</i> 2.6 (2.0, 3.3) at 0-60+y <i>Mild ID:</i> 1.8 (1.1, 2.7) at 0-60+y <i>Moderate ID:</i> 1.5 (1.1, 2.0) at 0-60+y <i>Severe ID:</i> 2.0 (1.5, 2.6) at 0-60+y <i>Profound ID:</i> 8.1 (5.6, 11.7) at 0-60+y	124 at 0-60+y; 112 at 20-60+y	<i>Underlying cause at 0-60+y:</i> Congenital anomalies: SMR=46.3 (32.9, 65.0) Nervous system: SMR=9.7 (5.5, 17.0) Mental disorder: SMR=4.0 (1.9, 8.4) Respiratory: SMR=3.3 (2.0, 5.5) Circulatory: SMR=2.1 (1.6, 2.7) Violent death: SMR=1.4 (0.6, 2.8) Neoplasm: SMR=0.9 (0.6, 1.6)
Durvasula & Beange (2002) ⁸	Australia	4.9 (3.4, 6.4) at 10-59y <i>M:</i> 4.1 (2.4, 5.9) at 10-59y <i>F:</i> 6.2 (3.3, 9.1) at 10-59y	40 at 10-59y; 31 at 20-59y	<i>Underlying cause at 10-59y:</i> Respiratory: 35% (pneumonia, aspiration) External causes: 20% Neoplasm: 17.5% Heart disease: 15% (congenital heart disease 50%) Gastrointestinal: 7.5% (ischaemic bowel, perforated peptic ulcer, post-operative peritonitis) Seizure: 5%
Tyrer et al (2007) ⁹	England	3.24 (2.93, 3.56) at 20-70+y <i>M:</i> 2.86 (2.50, 3.26) at 20-70+y <i>F:</i> 3.63 (3.12, 4.20) at 20-70+y 1.51 (1.23, 1.83) to 11.50 (8.14, 15.78) at 20-70+y <i>M:</i> 1.39 (1.03, 1.82) to 8.83 (5.60, 13.25) at 20-70+y <i>F:</i> 1.60 (1.18, 2.12) to 17.22 (9.64, 28.4) at 20-70+y <i>With Down syndrome:</i> 7.60 at 20-70+y <i>Without Down syndrome:</i> 2.70 at 20-70+y	409 at 20-70+y	Not reported
Patja et al (2008) ¹⁰	Finland	<i>M:</i> 2.2 at 20-39y, 1.0 at 40-59y, 1.0 at 60+y <i>F:</i> 1.4 at 20-39y, 1.1 at 40-49y, 1.0 at 60+y <i>Mild ID:</i> <i>M:</i> 1.6 at 20-39y, 1.0 at 40-59y, 1.0 at 60+y <i>F:</i> 1.2 at 20-39y, 1.1 at 40-49y, 1.0 at 60+y	1,046 at 20-97y	<i>Underlying cause at 2-97y:</i> Vascular: 36% (cardiac infarct 33%, cerebral infarct 33%, congenital heart disease 18%, pulmonary infarct 6%) Respiratory: 22% (pneumonia 83%, COPD 11%)

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		<p><i>Moderate ID:</i> M: 2.3 at 20-39y, 1.1 at 40-59y, 1.0 at 60+y F: 1.5 at 20-39y, 1.1 at 40-49y, 1.0 at 60+y</p> <p><i>Severe ID:</i> M: 2.6 at 20-39y, 1.2 at 40-59y, 1.0 at 60+y F: 1.6 at 20-39y, 1.0 at 40-49y, 1.0 at 60+y</p> <p><i>Profound ID:</i> M: 2.1 at 20-39y, 1.1 at 40-59y, 1.0 at 60+y F: 1.3 at 20-39y, 1.2 at 40-49y, 1.0 at 60+y</p>		<p>Neoplasm: 11% (digestive 44%, respiratory 15%, urogenital, 12%) Digestive: 7% (intestinal obstruction 25%, ulcer perforation 13%) Accidents and poisonings: 7% (commonest was fatal fracture, then drowning) Vascular, neoplasm, and accident causes were less common than sex-age-matched general population; Digestive were 2.5 times, Respiratory 2.6-5.8 times more common</p>
Tyrer & McGother (2009) ¹¹	England	<p>2.77 (2.53, 3.03) at 20+y M: 2.28 (2.02, 2.56) at 20+y F: 3.24 (2.83, 3.69) at 20+y</p>	503 at 20+y	<p><i>Underlying cause at 20+y:</i> Pneumonia: 13.1%, SMR=6.47 (5.00, 8.23) Nervous system: 13.1%, SMR=16.30 (12.61, 20.74) Other respiratory: 12.9%, SMR=4.64 (3.58, 5.91) Ischaemic heart disease: 11.5%, SMR=1.49 (1.13, 1.92) Neoplasm: 9.3% Congenital anomalies: 9.1%, SMR=85.60 (62.67, 114.18) Cerebrovascular disease: 7.8%, SMR=2.40 (1.71, 3.28)</p>
Oullette-Kuntz et al (2015) ¹²	Canada	<p>2.5 (2.1, 2.9) at 0-60+y M: 2.1 (1.7, 2.6) at 0-60+y F: 3.0 (2.4, 3.8) at 0-60+y M: 1.7 (1.3, 2.3) to 3.4 (2.3, 4.7) at 20-60+y F: 2.1 (1.4, 2.9) to 6.1 (4.1, 8.6) at 20-60+y</p>	172 at 0-60+y; 158 at 20-60+y	<p><i>Risk factors for death:</i> Age, Down syndrome (OR=1.76 at 20-39y; OR=1.69 at 40-59y; OR=22.34 at 60+y), cerebral palsy (OR=2.39 at 20-39y; OR=0.93 at 40-59y; OR=0.50 at 60+y), blindness/low vision (OR not given), technological dependence/medical fragility (OR=11.96 at 20-39y; OR=7.28 at 40-59y; OR=3.42 at 60+y), wheelchair dependence (OR=5.96 at 20-39y; OR=2.89 at 40-59y; OR=2.56 at 60+y), mobility impairment without wheelchair dependence (OR not given), epilepsy (OR=1.83 at 20-39y; OR=1.80 at 40-59y; OR=1.09 at 60+y)</p>
Florio & Troller (2015) ¹³	Australia	<p>2.48 (2.32, 2.64) at 0-85+y 3.15 (2.94, 3.38) at 5-69y M: 2.52 (2.29, 2.77) at 5-69y F: 4.26 (3.83, 4.74) at 5-69y</p>	953 at 0-85+y; 831 at 15+y	Not reported
McCarron et al (2015) ¹⁴	Republic of Ireland	<p>3.85 (3.70, 4.00) at 0-80+y M: 3.09 (2.93, 3.25) at 0-80+y F: 4.90 (4.63, 5.17) at 0-80+y 2.71 (2.41, 3.04) to 6.09 (5.29, 6.96) at 20-80y M: 2.50 (2.18, 2.86) to 4.50 (3.69, 5.44) at 20-80y F: 2.71 (2.32, 3.14) to 10.07 (8.99, 13.10) at 20-80y</p>	2,666 at 0-80+y; 2,394 at 20-80+y	Not reported

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1 2 3 4	Heslop & Glover (2015) ¹⁵	England	Median 2.13 (interquartile range 1.09, 2.83) across geographic areas at 18-65+y	18-65+y	Not reported
5 6 7 8 9 10 11	Lauer & McCallion (2015) ¹⁶	USA	<i>Intellectual and developmental disabilities*</i> : 1.19 at all ages, 2011 1.49 at 18+y, 2009	120,913 in 2009 at 18+y, 140,104 in 2011 at all ages	Not reported
12 13 14 15 16 17 18 19 20 21	Arvio et al (2016) ¹⁷	Finland	<i>Mild ID</i> : 2.28 (2.18, 2.39) at 0-60+y 1.99 (1.85, 2.13) to 2.77 (2.36, 3.23) at 15-60+y <i>M</i> : 2.01 (1.88, 2.14) at 0-60+y <i>F</i> : 2.80 (2.60, 3.01) at 0-60+y <i>Severe ID</i> : 3.41 (3.30, 3.52) at 0-60+y 2.07 (1.96, 2.19) to 8.77 (7.77, 9.87) at 15-60+y <i>M</i> : 2.59 (2.48, 2.72) at 0-60+y <i>F</i> : 5.24 (4.99, 5.50) at 0-60+y	5,171 at 0-60+y; 5,053 at 15-60y	Not reported
22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46	Hosking et al (2016) ⁵	England	HR=3.62 (3.33, 3.93) at 18-84y <i>M</i> : HR=3.30 (2.96, 3.68) at 18-84y <i>F</i> : HR=4.10 (3.61, 4.66) at 18-84y <i>With Down syndrome</i> : HR=9.21 (7.22, 11.76) <i>Without Down syndrome</i> : HR=3.19 (2.92, 3.49) <i>With epilepsy</i> : HR=6.04 (5.04, 7.24) <i>Without epilepsy</i> : HR=3.18 (2.90, 3.50) <i>With high level of support needs</i> : HR=4.77 (4.08, 5.59) <i>Without high level of support needs</i> : HR=3.28 (2.98, 3.62) <i>With autism</i> : HR=2.39 (1.45, 3.96) <i>Without autism</i> : HR=3.66 (3.37, 3.98) <i>In communal/shared homes</i> : HR=4.99 (4.36, 5.73) <i>Not in communal/shared homes</i> : HR=3.05 (2.74, 3.30)	656 at 18-84y	<i>Underlying cause at 18-84y</i> : Circulatory: 21.6%, HR=3.05 (2.56, 3.64) Respiratory: 18.8% (pneumonia and aspiration pneumonia), HR=6.68 (5.38, 8.29) Neoplasm: 14.9%, HR=1.44 (1.18, 1.76) Nervous system: 11.6%, HR=13.79 (9.70, 19.62) Digestive: 7.0%, HR=4.02 (2.92, 5.54) Congenital anomalies: 6.9%, HR could not be estimated Mental disorders: 5.3%, HR=7.99 (5.19, 12.31) External causes: 4.1%, HR=1.85 (1.26, 2.71) Genitourinary: 3.5%, HR=10.89 (6.09, 19.47) Endocrine, nutritional, and metabolic: 2.0%, HR=5.38 (2.79, 10.07) <i>Down syndrome</i> : Respiratory: 20.3% (or 42.4% if "Down syndrome" is excluded as an underlying cause of death) <i>Avoidable deaths</i> : 37% amenable (23% controls), 19% preventable (40% controls)

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Lauer (2016) ¹⁸	USA	Not reported	438 in 2012, 409 in 2013, at 18+y	<i>Major cause of death, 2012, 2013</i> Heart disease: 16.0%, 13.7% Neoplasm: 13.7%, 13.4% Alzheimer disease: 13.0%-12.2% (48% in Down syndrome) Aspiration pneumonia: 9.4%, 8.6% Septicaemia: 10.0%, 8.6% Chronic lower respiratory diseases: 4.6%, 6.6% Unintentional injury: 4.8%, 3.2%
Troller et al (2017) ¹⁹	Australia	1.3 (1.2, 1.5) at 20+y 4.0 (3.1, 5.2) at 20-44y 2.3 (2.0, 2.7) at 45-64y 1.0 (0.8, 1.2) at 65+y M: 1.4 (1.1, 1.6) at 20+y F: 1.3 (1.1, 1.6) at 20+y	732 at 20-65+y	<i>Underlying cause at 20-65+y:</i> Circulatory: 18% Neoplasm: 18% Nervous: 16% Respiratory: 12% Congenital anomaly: 11% Injury and poisoning: 6% Digestive: 5% <i>Avoidable deaths: 31%</i>
Glover et al (2017) ⁶	England	3.18 (2.94, 3.43) at 0-99y M: 3.03 (2.73, 3.35) at 0-99y F: 3.40 (3.02, 3.81) at 0-99y 1.6 (1.2, 2.1) to 7.8 (5.4, 11.1) at 18-99y M: 1.5 (0.9, 2.2) to 6.6 (4.0, 10.1) at 18-99y F: 1.7 (1.1, 2.4) to 11.6 (6.0, 20.2) at 18-99y	664 at 0-99y	<i>Underlying cause at 0-99y:</i> Circulatory: 22.9% (ischaemic heart disease 37.5%, cerebrovascular 25.7%, thrombophlebitis 6.6%, cardiomyopathy 5.9%, PE 3.9%), SMR=2.8 (2.4, 3.3) Respiratory: 17.2% (pneumonia 50.0%, pneumonitis 21.0%), SMR=4.9 (4.0, 5.9) Neoplasm: 3.1% (digestive 36.8%, respiratory 13.8%, female genital tract 10.3%, lymphoid and haematopoietic 10.3%), SMR=1.1 (0.9, 1.4) Nervous: 12.8%, SMR=9.8 (7.8, 12.1) Congenital anomalies: 8.4%, SMR=72.9 (55.1, 94.7) Digestive: 7.8%, SMR=4.0 (3.0, 5.2) No ICD10 chapters had fewer than expected deaths Other common single causes: dementia 33/664, epilepsy 26/664, cerebral palsy 23/664 <i>Avoidable deaths:</i> 44.7% (41.0%, 48.5%), mostly amenable M: 50.9% (45.9%, 56.0%); F: 36.9% (31.5%, 42.5%)

COPD=chronic obstructive pulmonary disease; HR=hazard ratio; ID=intellectual disabilities; OR=odds ratio; PE=pulmonary embolism; SMR=standardised mortality ratio; y=years

*Includes some individuals with IQ>70

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Supplementary table 2. Groupings of related causes of deaths

	ICD10
Infectious diseases	
Infection	
ENTEROCOLITIS DUE TO CLOSTRIDIUM DIFFICILE	A047
SEPSIS DUE TO STAPHYLOCOCCUS AUREUS	A410
SEPSIS, UNSPECIFIED	A419
BACTERIAL INFECTION, UNSPECIFIED	A499
SUBACUTE SCLEROSING PANENCEPHALITIS	A811
CHRONIC VIRAL HEPATITIS B WITHOUT DELTA-AGENT	B181
PULMONARY CANDIDIASIS	B371
NECROTISING FASCIITIS	M726
URINARY TRACT INFECTION, SITE NOT SPECIFIED	N390
Neoplasms	
Gastrointestinal malignant neoplasms	
MALIGNANT NEOPLASM OF PAROTID GLAND	C07
MALIGNANT NEOPLASM, OESOPHAGUS, UNSPECIFIED	C159
MALIGNANT NEOPLASM, STOMACH, UNSPECIFIED	C169
MALIGNANT NEOPLASM, CAECUM	C180
MALIGNANT NEOPLASM, SIGMOID COLON	C187
MALIGNANT NEOPLASM, COLON, UNSPECIFIED	C189
INTRAHEPATIC BILE DUCT CARCINOMA	C221
NEOPLASM OF UNCERTAIN OR UNKNOWN BEHAVIOUR, OTHER DIGESTIVE ORGANS	D377
Other neoplasms	
MALIGNANT NEOPLASM, LOWER LOBE, BRONCHUS OR LUNG	C343
MALIGNANT NEOPLASM, BRONCHUS OR LUNG, UNSPECIFIED	C349
MALIGNANT NEOPLASM, BREAST, UNSPECIFIED	C509
MALIGNANT NEOPLASM, ENDOMETRIUM	C541
MALIGNANT NEOPLASM OF OVARY	C56
MALIGNANT NEOPLASM, TESTIS, UNSPECIFIED	C629
MALIGNANT NEOPLASM, BLADDER, UNSPECIFIED	C679
MALIGNANT NEOPLASMS OF THYROID GLAND	C73
WALDENSTROM MACROGLOBULINAEMIA	C880
NON-HODGKIN'S LYMPHOMA, UNSPECIFIED	C859
MALIGNANT NEOPLASM OF UNSPECIFIED SITE	C80
NEOPLASM OF UNCERTAIN OR UNKNOWN BEHAVIOUR, TRACHEA, BRONCHUS AND LUNG	D381
SECONDARY MALIGNANT NEOPLASM OF LUNG	C780
SECONDARY MALIGNANT NEOPLASM OF LIVER AND INTRAHEPATIC BILE DUCT	C787
SECONDARY MALIGNANT NEOPLASM OF BRAIN AND CEREBRAL MENINGES	C793
SECONDARY MALIGNANT NEOPLASM OF OTHER SPECIFIED SITES	C798
Endocrine and metabolic diseases	
Diabetes	
INSULIN-DEPENDENT DIABETES MELLITUS WITHOUT COMPLICATIONS	E109
NON-INSULIN-DEPENDENT DIABETES MELLITUS WITH RENAL COMPLICATIONS	E112
NON-INSULIN-DEPENDENT DIABETES MELLITUS W. PERIPHERAL CIRC. COMPLICATIONS	E115
NON-INSULIN-DEPENDENT DIABETES MELLITUS WITHOUT COMPLICATIONS	E119
UNSPECIFIED DIABETES MELLITUS WITH RENAL COMPLICATIONS	E142

Rates, causes, place, and predictors of mortality in adults with intellectual disabilities with and without Down syndrome: cohort study with record linkage

1		
2	UNSPECIFIED DIABETES MELLITUS WITHOUT COMPLICATIONS	E149
3	ABNORMAL GLUCOSE TOLERANCE TEST	R730
4	HYPERGLYCAEMIA, UNSPECIFIED	R739
5		
6	Metabolic disorders	
7	OTHER HYPERPHENYLALANINAEMIAS	E701
8	DISORDERS OF PHOSPHORUS METABOLISM & PHOSPHATASES	E833
9	DISORDERS OF PLASMA-PROTEIN METABOLISM, NOT ELSEWHERE CLASSIFIED	E880
10		
11		
12	Mental disorders	
13	Dementias	
14	VASCULAR DEMENTIA, UNSPECIFIED	F019
15	UNSPECIFIED DEMENTIA	F03
16	ALZHEIMER'S DISEASE WITH LATE ONSET	G301
17	ALZHEIMER'S DISEASE, UNSPECIFIED	G309
18		
19	Mental health	
20	MENTAL AND BEHAVIOURAL DISORDERS DUE TO ACUTE INTOXICATION WITH ALCOHOL	F100
21	MENTAL AND BEHAVIOURAL DISORDERS DUE TO ALCOHOL DEPENDENCE SYNDROME	F102
22	MENTAL AND BEHAVIOURAL DISORDERS DUE TO USE OF TOBACCO, UNSPECIFIED	F179
23	SCHIZOPHRENIA, UNSPECIFIED	F209
24	BIPOLAR AFFECTIVE DISORDER, UNSPECIFIED	F319
25	OTHER & UNSPEC SYMPTOMS & SIGNS INVOLVING COGNITIVE FUNCTIONS &	R418
26	AWARENESS	
27	INTENTIONAL SELF-HARM BY JUMPING FROM A HIGH PLACE	X80
28		
29	Intellectual disabilities	
30	UNSPECIFIED MENTAL RETARDATION	F79
31	DEVELOPMENTAL DISORDER OF SCHOLASTIC SKILLS, UNSPECIFIED	F819
32		
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35	Nervous system	
36	Epilepsies	
37	GENERALIZED IDIOPATHIC EPILEPSY AND EPILEPTIC SYNDROMES	G403
38	EPILEPSY, UNSPECIFIED	G409
39	STATUS EPILEPTICUS, UNSPECIFIED	G419
40	MYOTONIC DISORDERS	G711
41	OTHER AND UNSPECIFIED CONVULSIONS	R568
42		
43	Cerebral palsy	
44	SPASTIC QUADRAPLEGIC CEREBRAL PALSY	G800
45	SPASTIC HEMIPLEGIC CEREBRAL PALSY	G802
46	OTHER CEREBRAL PALSY	G808
47	CEREBRAL PALSY, UNSPECIFIED	G809
48	TETRAPLEGIA, UNSPECIFIED	G825
49		
50	Other neurological conditions	
51	SEQUELAE OF INFLAMMATORY DISEASES OF CENTRAL NERVOUS SYSTEM	G09
52	PARKINSON'S DISEASE	G20
53	MYONEURAL DISORDER, UNSPECIFIED	G709
54	ENCEPHALITIS, MYELITIS AND ENCEPHALOMYELITIS, UNSPECIFIED	G049
55	ANOXIC BRAIN DAMAGE, NOT ELSEWHERE CLASSIFIED	G931
56	BLINDNESS, BINOCULAR	H540
57	OTHER DISORDERS OF NERVOUS SYSTEM, NOT ELSEWHERE CLASSIFIED	G98
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Rates, causes, place, and predictors of mortality in adults with intellectual disabilities with and without Down syndrome: cohort study with record linkage

Circulatory system

Acute myocardial infarction

ACUTE MYOCARDIAL INFARCTION, UNSPECIFIED I219

CARDIAC ARRECT, UNSPECIFIED I469

Other ischaemic heart disease

HYPERTENSIVE HEART DISEASE WITHOUT (CONGESTIVE) HEART FAILURE I119

ACUTE ISCHAEMIC HEART DISEASE, UNSPECIFIED I249

ATHEROSCLEROTIC HEART DISEASE I251

CHRONIC ISCHAEMIC HEART DISEASE, UNSPECIFIED I259

ATHEROSCLEROSIS OF AORTA I700

GENERALIZED AND UNSPECIFIED ATHEROSCLEROSIS I709

Heart failure

HEART FAILURE, UNSPECIFIED I509

LEFT VENTRICULAR FAILURE I501

CONGESTIVE HEART FAILURE I500

Other cardiovascular disease

PULMONARY EMBOLISM WITHOUT MENTION OF ACUTE COR PULMONALE I269

OTHER SPECIFIED PULMONARY HEART DISEASES I278

PULMONARY HEART DISEASE, UNSPECIFIED I279

AORTIC (VALVE) STENOSIS I350

ATRIAL FIBRILLATION AND FLUTTER I48

VENTRICULAR FIBRILLATION AND FLUTTER I490

OTHER ILL-DEFINED HEART DISEASES I518

PULMONARY OEDEMA J81

CARDIOGENIC SHOCK R570

PERIPHERAL VASCULAR DISEASE, UNSPECIFIED I739

PHLEBITIS AND THROMBOPHLEBITIS OF OTHER DEEP VESSELS OF LOWER EXTREMITIES I802

EMBOLISM AND THROMBOSIS OF OTHER SPECIFIED VEINS I828

ACUTE AND SUBACUTE INFECTIVE ENDOCARDITIS I330

ACUTE ENDOCARDITIS, UNSPECIFIED I339

ENDOCARDITIS, VALVE UNSPECIFIED I38

DILATED CARDIOMYOPATHY I420

CARDIOMEGALY I517

ESSENTIAL (PRIMARY) HYPERTENSION I10

Stroke

INTRACEREBRAL HAEMORRHAGE, UNSPECIFIED I619

CEREBRAL INFARCTION DUE TO THROMBOSIS OF PRECEREBRAL ARTERIES I630

CEREB INFARCT DUE TO UNSPEC OCCL/STENOSIS OF PRECEREB ARTERIES I632

CEREBRAL INFARCTION, UNSPECIFIED I639

STROKE, NOT SPECIFIED AS HAEMORRHAGE OR INFARCTION I64

CEREBROVASCULAR DISEASE, UNSPECIFIED I679

SEQUELAE OF STROKE, NOT SPECIFIED AS HAEMORRHAGE OR INFARCTION I694

SEQUELAE OF OTHER AND UNSPECIFIED CEREBROVASCULAR DISEASES I698

Respiratory system

Respiratory infection

ACUTE UPPER RESPIRATORY INFECTION, UNSPECIFIED J069

INFLUENZA WITH PNEUMONIA, OTHER INFLUENZA VIRUS IDENTIFIED J100

INFLUENZA WITH OTHER RESP MANIFESTATIONS, OTHER INFLUENZA VIRUS IDENTIFIED J101

Rates, causes, place, and predictors of mortality in adults with intellectual disabilities with and without Down syndrome: cohort study with record linkage

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2	PNEUMONIA DUE TO STREPTOCOCCUS PNEUMONIAE	J13
3	BRONCHOPNEUMONIA, UNSPECIFIED	J180
4	LOBAR PNEUMONIA, UNSPECIFIED	J181
5	HYPOSTATIC PNEUMONIA, UNSPECIFIED	J182
6	PNEUMONIA, UNSPECIFIED	J189
7	UNSPECIFIED ACUTE LOWER RESPIRATORY INFECTION	J22
8	CHRONIC OBSTRUCTIVE PULMONARY DISEASE WITH ACUTE LOWER RESP INFECTION	J440
9		
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11	Aspiration/reflux/choking	
12	PNEUMONITIS DUE TO FOOD AND VOMIT	J690
13	GASTRO-OESOPHAGEAL REFLUX DISEASE WITHOUT OESOPHAGITIS	K219
14	INHALATION AND INGESTION OF FOOD CAUSING OBSTRUCTION OF RESPIRATORY	W79
15	TRACT	
16	FOREIGN BODY IN RESPIRATORY TRACT, PART UNSPECIFIED	T179
17	INHALATION/INGESTION OF OTHER OBJECTS CAUSING OBSTRUCT OF RESP TRACT	W80
18		
19	Other respiratory disorders	
20	UNSPECIFIED CHRONIC BRONCHITIS	J42
21	EMPHYSEMA, UNSPECIFIED	J439
22	CHRONIC OBSTRUCTIVE PULMONARY DISEASE, UNSPECIFIED	J440
23	ASTHMA, UNSPECIFIED	J459
24	BRONCHIECTASIS	J47
25	OTHER INTERSTITIAL PULMONARY DISEASES WITH FIBROSIS	J841
26	PLEURAL EFFUSION, NOT ELSEWHERE CLASSIFIED	J90
27	CHRONIC RESPIRATORY FAILURE	J961
28	RESPIRATORY FAILURE, UNSPECIFIED	J969
29	OTHER SPECIFIED RESPIRATORY DISORDERS	J988
30	DYSPNOEA	R060
31	RESPIRATORY ARREST	R092
32	ASPHYXIATION	T71
33	UNSPECIFIED THREAT TO BREATHING	W84
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39	Digestive system	
40	Ulcer/gastrointestinal perforation	
41	OESOPHAGITIS	K20
42	PERFORATION OF INTESTINE (NONTRAUMATIC)	K631
43	PERITONITIS, UNSPECIFIED	K659
44	GASTRIC ULCER, CHRONIC OR UNSPECIFIED WITH PERFORATION	K255
45	OTHER PERITONITIS	K658
46	ACUTE PERITONITIS	K650
47	GASTROINTESTINAL HAEMORRHAGE, UNSPECIFIED	K922
48	ULCER OF INTESTINE	K633
49		
50	Other gastrointestinal disorders	
51	BARRETTS OESOPHAGUS	K227
52	DIAPHRAGMATIC HERNIA WITHOUT OBSTRUCTION OR GANGRENE	K449
53	OTHER SPECIFIED NONINFECTIVE GASTROENTERITIS AND COLITIS	K528
54	ACUTE VASCULAR DISORDERS OF INTESTINE	K550
55	VASCULAR DISORDER OF INTESTINE, UNSPECIFIED	K559
56	VOLVULUS	K562
57	OTHER AND UNSPECIFIED INTESTINAL OBSTRUCTION	K566
58	CONSTIPATION	K590
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Rates, causes, place, and predictors of mortality in adults with intellectual disabilities with and without Down syndrome: cohort study with record linkage

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2	MEGACOLON, NOT ELSEWHERE CLASSIFIED	K593
3	ACUTE AND SUBACUTE HEPATIC FAILURE	K720
4	OTHER AND UNSPECIFIED CIRRHOSIS OF LIVER	K746
5	AUTOIMMUNE HEPATITIS	K754
6	INFLAMMATORY LIVER DISEASE, UNSPECIFIED	K759
7	OTHER SPECIFIED DISEASES OF LIVER	K768
8	CALCULUS OF GALLBLADDER WITH OTHER CHOLECYSTITIS	K801
9	CHOLANGITIS	K830
10	ACUTE PANCREATITIS, UNSPECIFIED	K859
11	PSEUDOCYST OF PANCREAS	K863
12	INTESTINAL MALABSORPTION, UNSPECIFIED	K909
13	DYSPHAGIA	R13

Genitourinary system

Renal failure

14	CHRONIC NEPHRITIC SYNDROME, UNSPECIFIED	N039
15	OTHER ACUTE RENAL FAILURE	N178
16	ACUTE RENAL FAILURE, UNSPECIFIED	N179
17	END-STAGE RENAL DISEASE	N180
18	CHRONIC KIDNEY DISEASE, STAGE 5	N185
19	CHRONIC KIDNEY DISEASE, UNSPECIFIED	N189
20	UNSPECIFIED KIDNEY FAILURE	N19

Chromosomal abnormalities

Down syndrome

21	DOWN'S SYNDROME, UNSPECIFIED	Q909
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Other congenital condition

22	CONGENITAL HYDROCEPHALUS, UNSPECIFIED	Q039
23	SPINA BIFIDA, UNSPECIFIED	Q059
24	CONGENITAL MALFORMATION OF HEART, UNSPECIFIED	Q249
25	CONGENITAL DEFORMITY OF SPINE	Q675
26	CONGEN MALFORMATION SYNDROMES PREDOMINANTLY ASSOCIATED WITH SHORT STATURE	Q871
27	MARFAN'S SYNDROME	Q874
28	OTHER SPECIFIED CONGEN MALFORMATION SYNDROMES, NOT ELSEWHERE CLASSIFIED	Q878
29	CONGENITAL MALFORMATION, UNSPECIFIED	Q899
30	KLINEFELTER'S SYNDROME, UNSPECIFIED	Q984
31	FRAGILE X CHROMOSOME	Q992
32	OTHER LACK OF EXPECTED NORMAL PHYSIOLOGICAL DEVELOPMENT	R628

Other conditions occurring with small frequency

Other condition

33	DECUBITUS ULCER AND PRESSURE AREA	L89
34	SCOLIOSIS, UNSPECIFIED	M419
35	URETHRAL STRICTURE, UNSPECIFIED	N359
36	EPISTAXIS	R040
37	IMMOBILITY	R263
38	MALAISE AND FATIGUE	R53
39	GENERALIZED ENLARGED LYMPH NODES	R591

Rates, causes, place, and predictors of mortality in adults with intellectual disabilities with and without Down syndrome: cohort study with record linkage

1		
2	INSUFFICIENT INTAKE OF FOOD AND WATER DUE TO SELF NEGLECT	R636
3	OTHER SPECIFIED GENERAL SYMPTOMS AND SIGNS	R688
4	OTHER ILL-DEFINED AND UNSPECIFIED CAUSES OF MORTALITY	R99
5	EXPOSURE TO UNSPECIFIED FACTOR	X59
6	MULTI-SYSTEM DEGENERATION	G903
7	BENIGN NEOPLASM, MENINGES, UNSPECIFIED	D329
8	AGRANULOCYTOSIS	D70
9	SARCOIDOSIS OF OTHER AND COMBINED SITES	D868
10	SARCOIDOSIS, UNSPECIFIED	D869
11	HYPOPITUITARISM	E230
12	HYPOTHYROIDISM, UNSPECIFIED	E039
13	OTHER THYROTOXICOSIS	E058
14	VOLUME DEPLETION	E86
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19	Injuries and external causes	
20	Injuries and accidents	
21	INTRACRANIAL INJURY, UNSPECIFIED	S069
22	UNSPECIFIED INJURY OF HEAD	S099
23	INJURY OF COLON	S365
24	FRACTURE OF NECK OF FEMUR	S720
25	FRACTURE OF SHAFT OF TIBIA	S822
26	UNSPECIFIED MULTIPLE INJURIES	T07
27	FAT EMBOLISM (TRAUMATIC)	T791
28	SEQUELAE OF UNSPECIFIED INJURY OF HEAD	T909
29	UNSPECIFIED FALL	W19
30	SEQUELAE OF OTHER ACCIDENTS	Y86
31	Medical/surgical complication	
32	POISONING BY OTHER ANTIDYSRHYTHMIC DRUGS, NOT ELSEWHERE CLASSIFIED	T462
33	ADVERSE EFFECTS OF OTHER ANTIDYSRHYTHMIC DRUGS, NOT ELSEWHERE CLASSIFIED	Y522
34	ABN REACT TO/LATER COMPLIC OF OP WITH IMPLANT OF ARTIFICIAL INTERN DEVICE	Y831
35	ABN REACT TO/LATER COMPLIC OF OP WITH ANASTOMOSIS, BYPASS OR GRAFT	Y832
36	ABN REACT TO/LATER COMPLIC OF OP WITH FORMATION OF EXTERNAL STOMA	Y833
37	ABNORMAL REACTION TO OR LATER COMPLICATION OF OTHER MEDICAL PROCEDURES	Y848
38	SEQ OF PROCED CAUSING ABN REACT/COMPLIC,W/O MENTION OF MISADV AT THE TIME	Y883
39	OTHER POSTPROCEDURAL RESPIRATORY DISORDERS	J958
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Rates, causes, place, and predictors of mortality in adults with intellectual disabilities with and without Down syndrome: cohort study with record linkage

Supplementary table 3. Predictors of the outcome time to death from univariate analyses

Variable		N with event/ N in group	Hazard ratio (95% CI)	Individual p-value	Overall p-value
Demographics					
Age at time of health assessment		294/961	1.05 (1.04, 1.06)	<0.0001	
Sex	Male	154/525	0.88 (0.70, 1.11)	0.2730	
	Female	140/436	1.00 (-)		
Ability level	Mild ID	92/382	1.00 (-)		0.0007
	Moderate ID	73/236	1.38 (1.01, 1.87)	0.0411	
	Severe ID	67/180	1.75 (1.28, 2.40)	0.0005	
	Profound ID	62/163	1.77 (1.28, 2.45)	0.0005	
Type of accommodation	Family carer	70/374	1.00 (-)		<0.0001
	Independent of care	36/93	2.35 (1.57, 3.52)	<0.0001	
	Paid support	161/435	2.18 (1.65, 2.88)	<0.0001	
	Congregate	27/59	2.87 (1.84, 4.48)	<0.0001	
Neighbourhood deprivation	1 - most affluent	18/73	1.00 (-)		0.1890
	2	56/137	1.92 (1.13, 3.27)	0.0158	
	3	10/45	0.90 (0.42, 1.95)	0.7896	
	4	10/40	1.06 (0.49, 2.30)	0.8808	
	5	12/32	1.71 (0.82, 3.55)	0.1527	
	6	9/32	1.27 (0.57, 2.82)	0.5640	
	7	9/34	1.09 (0.49, 2.43)	0.8302	
	8	15/58	1.21 (0.61, 2.41)	0.5818	
	9	35/124	1.22 (0.69, 2.16)	0.4882	
	10 - most deprived	120/386	1.41 (0.86, 2.31)	0.1782	
Civil status	Single	288/938	1.28 (0.57, 2.87)	0.5485	
	Not single	6/23	1.00 (-)		
Employment/day activities	Yes	83/231	1.33 (1.03, 1.71)	0.0284	
	No	211/730	1.00 (-)		
Smoker	Yes	46/101	1.70 (1.24, 2.33)	0.0009	
	No	248/860	1.00 (-)		
Health					
Down syndrome	Yes	64/179	1.30 (0.98, 1.71)	0.0673	
	No	230/782	1.00 (-)		
Epilepsy	Yes	111/325	1.25 (0.99, 1.58)	0.0636	
	No	183/636	1.00 (-)		
Spastic quadriplegia	Yes	24/325	1.67 (1.10, 2.54)	0.0158	
	No	183/636	1.00 (-)		
Impaired mobility	Yes	195/735	0.51 (0.40, 0.65)	<0.0001	
	No	99 /226	1.00 (-)		
Body mass index	Underweight	9/43	0.63 (0.32, 1.25)	0.1847	0.1865
	Acceptable	83/265	1.00 (-)		
	Overweight	75/289	0.78 (0.57, 1.06)	0.1132	
	Obese	81/237	1.08 (0.80, 1.47)	0.6152	
	Morbidly obese	16/58	0.87 (0.51, 1.48)	0.6058	
Hearing impairment	Yes	112/267	1.79 (1.41, 2.26)	<0.0001	
	No	182/694	1.00 (-)		
Visual impairment	Yes	154/449	1.29 (1.02, 1.62)	0.0317	
	No	140/512	1.00 (-)		

Rates, causes, place, and predictors of mortality in adults with intellectual disabilities with and without Down syndrome: cohort study with record linkage

Urinary incontinence	Yes	158/632	0.52 (0.41, 0.65)	<0.0001	
	No	136/329	1.00 (-)		
Bowel incontinence	Yes	197/733	0.55 (0.43, 0.70)	<0.0001	
	No	97/228	1.00 (-)		
Diabetes	Yes	29/47	2.72 (1.86, 4.00)	<0.0001	
	No	265/914	1.00 (-)		
PEG/tube fed	Yes	N/7	4.99 (2.22, 11.20)	0.0001	
	No	288/954			
Constipation	Yes	112/316	1.34 (1.06, 1.70)	0.0145	
	No	182/645	1.00 (-)		
Ataxia/gait disorder	Yes	104/276	1.50 (1.18, 1.90)	0.0009	
	No	190/685	1.00 (-)		
Nail disorder	Yes	74/223	1.18 (0.91, 1.54)	0.2120	
	No	220/738	1.00 (-)		
Epidermal thickening	Yes	66/207	1.10 (0.84, 1.45)	0.4947	
	No	228/754	1.00 (-)		
Cerebral palsy	Yes	54/175	1.02 (0.76, 1.37)	0.8792	
	No	240/786	1.00 (-)		
Osteoporosis	Yes	76/174	1.71 (1.32, 2.22)	<0.0001	
	No	218/786	1.00 (-)		
Fungal infection	Yes	42/158	0.83 (0.61, 1.18)	0.3366	
	No	252/803	1.00 (-)		
Hypertension	Yes	56/146	1.36 (1.01, 1.82)	0.0399	
	No	238/815	1.00 (-)		
Dysphagia	Yes	51/132	1.51 (1.11, 2.04)	0.0080	
	No	243/829	1.00 (-)		
Dyspnoea	Yes	49/130	1.41 (1.04, 1.92)	0.0285	
	No	245/831	1.00 (-)		
Musculoskeletal pain	Yes	48/148	1.14 (0.83, 1.55)	0.4153	
	No	246/813	1.00 (-)		
Bone deformity	Yes	50/139	1.32 (0.97, 1.79)	0.0769	
	No	244/822	1.00 (-)		
Dental/oral problem	Yes	38/120	1.07 (0.76, 1.50)	0.7128	
	No	256/841	1.00 (-)		
Eczema/dermatitis	Yes	38/138	0.86 (0.61, 1.21)	0.3790	
	No	256/823	1.00 (-)		
GORD	Yes	51/133	1.43 (1.06, 1.94)	0.0198	
	No	243/828	1.00 (-)		
Lower respiratory tract infection	Yes	55/126	1.75 (1.30, 2.34)	0.0002	
	No	239/835	1.00 (-)		
Total number of physical conditions		294/961	1.06 (1.04, 1.08)	<0.0001	
Psychosis	Yes	11 /42	0.81 (0.44, 1.48)	0.4990	
	No	283 /919	1.00 (-)		
Affective disorder including bipolar	Yes	24/68	1.19 (0.78, 1.80)	0.4216	
	No	270/893	1.00 (-)		
Autism	Yes	13/69	0.54 (0.31, 0.94)	0.0306	
	No	281/892	1.00 (-)		
Problem behaviour	Yes	71/218	1.09 (0.83, 1.42)	0.5251	
	No	223/743	1.00 (-)		
Eating disorder, including pica	Yes	5/17	0.99 (0.41, 2.40)	0.9857	
	No	289/944	1.00 (-)		
Any mental illness, excluding problem behaviours	Yes	73/217	1.16 (0.89, 1.51)	0.2849	
	No	221/744	1.00 (-)		
Service use					
Number of GP consultations in last 12 months		287/951	1.05 (1.03, 1.06)	<0.0001	

Rates, causes, place, and predictors of mortality in adults with intellectual disabilities with and without Down syndrome: cohort study with record linkage

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Number of A&E attendances in last 12 months		280/938	1.09 (0.99, 1.20)	0.0847	
Number of health professions providing care		294/961	1.10 (1.03, 1.16)	0.0023	
Prescriptions					
Antipsychotics	Yes	79/226	1.12 (0.94, 1.57)	0.1421	
	No	215/735	1.00 (-)		
Antidepressants	Yes	39/118	1.16 (0.83, 1.63)	0.3778	
	No	255/843	1.00 (-)		
Anxiolytic/hypnotics	Yes	20/68	0.95 (0.60, 1.49)	0.8159	
	No	274/893	1.00 (-)		
Antiepileptics	Yes	90/253	1.31 (1.02, 1.68)	0.0315	
	No	204/708	1.00 (-)		
Number of drug classes taken		294/961	1.16 (1.12, 1.21)	<0.0001	

A&E=accident and emergency; CI=confidence interval; GORD=gastro-oesophageal reflux disorder; PEG=percutaneous endoscopic gastrostomy

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No.	Recommendation	Page No.	Relevant text from manuscript
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract		p1
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found		p2
Introduction				
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported		p4-6, supplementary table 1
Objectives	3	State specific objectives, including any prespecified hypotheses		6, paragraph 3
Methods				
Study design	4	Present key elements of study design early in the paper		p6-10, supplementary tables 2/3
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection		p7, paragraph 1, 7-8
Participants	6	(a) <i>Cohort study</i> —Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up <i>Case-control study</i> —Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls <i>Cross-sectional study</i> —Give the eligibility criteria, and the sources and methods of selection of participants		p7, paragraph 1
		(b) <i>Cohort study</i> —For matched studies, give matching criteria and number of exposed and unexposed <i>Case-control study</i> —For matched studies, give matching criteria and the number of controls per case		p7, paragraph 2, p9, paragraph 4
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable		p7-8, supplementary table 2
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group		p7-8, p9, paragraph 4
Bias	9	Describe any efforts to address potential sources of bias		p9, paragraph 4
Study size	10	Explain how the study size was arrived at		P7, paragraph2, p9, paragraph 4

Continued on next page

Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	p8-10
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	p8-10
		(b) Describe any methods used to examine subgroups and interactions	p8-10
		(c) Explain how missing data were addressed	p11, paragraph 2
		(d) <i>Cohort study</i> —If applicable, explain how loss to follow-up was addressed	p11, paragraph 2
		<i>Case-control study</i> —If applicable, explain how matching of cases and controls was addressed	
		<i>Cross-sectional study</i> —If applicable, describe analytical methods taking account of sampling strategy	
		(e) Describe any sensitivity analyses	N/A
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	p11, paragraph 2
		(b) Give reasons for non-participation at each stage	p11, paragraph 2
		(c) Consider use of a flow diagram	-
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	p11-12, Table 1, supplementary table 3
		(b) Indicate number of participants with missing data for each variable of interest	table 1, supplementary table 3
		(c) <i>Cohort study</i> —Summarise follow-up time (eg, average and total amount)	p12, paragraph 1
Outcome data	15*	<i>Cohort study</i> —Report numbers of outcome events or summary measures over time	p11, paragraph 2
		<i>Case-control study</i> —Report numbers in each exposure category, or summary measures of exposure	
		<i>Cross-sectional study</i> —Report numbers of outcome events or summary measures	
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	P15, table 6
		(b) Report category boundaries when continuous variables were categorized	N/A
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	-

Continued on next page

Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	p11-16
Discussion			
Key results	18	Summarise key results with reference to study objectives	p16, paragraph 2
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	p20, paragraph 1
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	p20, paragraph 2
Generalisability	21	Discuss the generalisability (external validity) of the study results	p20, paragraph 1
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	P24

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

Rates, causes, place, and predictors of mortality in adults with intellectual disabilities with and without Down syndrome: cohort study with record linkage

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3 **Rates, causes, place, and predictors of mortality in**
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6 **adults with intellectual disabilities with and without**
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9 **Down syndrome: cohort study with record linkage**
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Abstract

Objectives

To investigate mortality in adults with intellectual disabilities: rates, causes, place, demographic and clinical predictors.

Design

Cohort study with record linkage to death data.

Setting

General community.

Participants

961/1,023 (94%) adults (16-83 years; mean=44.1 years; 54.6% male) with intellectual disabilities, clinically examined in 2001-2004; subsequently record-linked to their National Health Service number, allowing linkage to death certificate data, 2018.

Outcome measures

Standardised mortality ratios (SMRs), underlying, and all contributing causes of death, avoidable deaths, place, and demographic and clinical predictors of death.

Results

294/961 (30.6%) had died; 64/179 (35.8%) with Down syndrome, 230/783 (29.4%) without Down syndrome. SMR overall=2.24 (1.98, 2.49); Down syndrome adults=5.28 (3.98, 6.57), adults without Down syndrome=1.93 (1.68, 2.18); male=1.69 (1.42, 1.95), female=3.48 (2.90, 4.06). SMRs decreased as age increased. More severe intellectual disabilities increased SMR, but ability was not retained in the multivariable model. SMRs were higher for most ICD-10 chapters. For adults without Down syndrome, aspiration/reflux/choking, and respiratory infection were the commonest underlying causes of mortality; for Down syndrome adults "Down syndrome", and dementia were most common. Amenable deaths (29.8%) were double that in the general population (14%). 60.3% died in hospital. Mortality risk related to: percutaneous endoscopic gastrostomy/tube fed, Down syndrome, diabetes, lower respiratory tract infection at

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3 cohort-entry, smoking, epilepsy, hearing impairment, increasing number of prescribed
4 drugs, increasing age. Bowel incontinence reduced mortality risk.

7 **Conclusions**

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9 Adults with intellectual disabilities with and without Down syndrome have different SMRs
10 and causes of death which should be separately reported. Both die younger, from
11 different causes than other people. Some mortality risks are similar to other people, with
12 earlier mortality reflecting more multi-morbidity; amenable deaths are also common.
13 This should inform actions to reduce early mortality, e.g. training to avoid
14 aspiration/choking, pain identification to address problems before they are advanced,
15 and reasonable adjustments to improve health-care quality.
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26 **Strengths and limitations of this study**

- 27 • Thorough methods of case ascertainment for intellectual disabilities at baseline.
- 28 • Individual verification of intellectual disabilities and its severity, and detailed health
29 assessments at baseline.
- 30 • Longitudinal design.
- 31 • Large cohort size and study duration, and successful record linkage for 94% of
32 participants.
- 33 • Limitations include that the study was conducted in only one part of Scotland, and
34 the reliance upon recorded cause of death from death certificates.
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49 Word count: 5,610
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Introduction

People with intellectual disabilities die at a younger age than other people; on average, 20 years younger,¹ or 28 years younger specifically for people with Down syndrome.² It has been demonstrated that people with intellectual disabilities receive poorer management of their long term conditions within primary health care services compared with the general population,³ and it is conceivable that this is one contributor to earlier mortality. It has been suggested that as many as 40% of deaths of people with intellectual disabilities may have been amenable to good quality health care.⁴⁻⁶ There has been a recent increase in research on mortality in people with intellectual disabilities, but very little research has distinguished people with intellectual disabilities with and without Down syndrome, or investigated the factors associated with risk of mortality, and causes of mortality.

Previous studies on death in people with intellectual disabilities had limitations such as small sample sizes, or non-representative populations. More recently, there have been large-scale studies which are more representative, having been drawn from intellectual disabilities registers, or social security or primary care data with record linkage to death certification. These have been undertaken in parts of Sweden, Australia, England, Finland, Canada, Ireland, and USA (supplementary table 1).⁵⁻¹⁹ These studies fairly consistently report standardised mortality ratios (SMRs) to be high for people with intellectual disabilities, more so at younger ages, and higher for women than men. Adult studies have tended to report SMRs in the region of 2-4, although in some, SMR is only slightly above 1.^{10,16,19} However, direct comparison between studies is not always possible, due to the different age ranges studied and methods of reporting.

- Supplementary table 1 -

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3 In view of the methods that studies have used for population identification (typically,
4 routine administrative data linked to death certifications), they provide little information
5 on the socio-clinical factors that influence SMR, or the risk factors associated with death,
6 beyond that of age and sex. Three studies reported SMR by level of intellectual
7 disabilities, with, broadly speaking, higher SMR with more severe intellectual
8 disabilities.^{7,10,17} Only three studies (different studies to those that reported on level of
9 intellectual disabilities) were able to report data separately for adults with intellectual
10 disabilities with and without Down syndrome; two found higher mortality rates for adults
11 with Down syndrome (SMR=7.6,⁹ and hazard ratio=9.21⁵) than for adults without Down
12 syndrome, or an odds ratio showing Down syndrome as a risk of death.¹² A further
13 study reported SMR=5.5 for children and adults (combined) with Down syndrome, but
14 did not report SMR for those with intellectual disabilities without Down syndrome.²⁰ Two
15 studies reported adults with intellectual disabilities to have higher SMRs if they have the
16 co-morbidities of epilepsy,^{5,7} and cerebral palsy,⁷ as opposed to not having these
17 comorbidities. One study reported adults with intellectual disabilities with comorbid
18 autism to have lower risk of mortality than those without comorbid autism.⁵ One study
19 reported the risk factors for mortality in a population with intellectual disabilities to be:
20 age, Down syndrome, cerebral palsy, blindness/low vision, technological
21 dependence/medical fragility, wheelchair dependence, mobility impairment without
22 wheelchair dependence, and epilepsy.¹² Factors not found to be risks, if any, were not
23 reported, and a further limitation was that factors were reported by agency staff, rather
24 than the individuals undergoing health assessments.¹² We have not identified any other
25 studies that investigated risk factors for time to mortality in adults with intellectual
26 disabilities.

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54 There is less consistency regarding the most common certified underlying causes of
55 death in adults with intellectual disabilities, partly as some studies do not report these
56 separately for children and adults, or by age ranges. Additionally, studies group causes
57 of death in different ways (e.g. pneumonia versus respiratory system), which can affect
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3 prevalence rankings between studies. Pneumonia, other respiratory diseases, and
4 diseases of the nervous system were reported to be the most common in one study,¹¹
5 diseases of the circulatory system and respiratory systems in another,⁵ heart disease,
6 neoplasm, and Alzheimer disease in a third,¹⁸ and diseases of the circulatory system,
7 neoplasm, and the nervous system in a fourth.¹⁹ In adults with intellectual disabilities,
8 cause specific SMRs have been reported to be high across most groups of disorders.^{5,11}
9 These studies did not report cause of death separately for adults with and without Down
10 syndrome. Given the different health profile of people with Down syndrome compared
11 with people with intellectual disabilities of other causes, this is an important limitation.²¹
12 In people with Down syndrome, most studies on mortality have been conducted with
13 child populations, and report the most common causes of death to be congenital heart
14 disease, and pneumonia/diseases of the respiratory system.²
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Overall, the existing body of literature on mortality in adults with intellectual disabilities does not include more detailed information on level of intellectual disabilities, nor separate out the population with, from those without, Down syndrome (for whom causes of death may differ), nor investigate health and demographic predictors of death other than age and sex, and is inconsistent with regards to causes of death. A better understanding of these factors may provide a pathway to action to reduce the observed earlier mortality in adults with intellectual disabilities.

This study aims to investigate the rates, causes, place, and demographic and clinical associations with mortality in adults with intellectual disabilities, with and without Down syndrome.

Methods

Approval

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3 Ethical approval was gained from NHS Greater Glasgow Primary Care Trust -
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5 Community & Mental Health Research Ethics Committee, and NHS Greater Glasgow and
6
7 Clyde Safe Haven. Individual consent to participate was taken in line with Scottish law,
8
9 between 2001-2004.
10

11 12 13 **Participants**

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15 The adult (aged 16+ years) intellectual disabilities population living within the NHS
16
17 Greater Glasgow area was identified through multiple sources between 2000-2001.
18
19 General practitioners were financially incentivised to identify their registered patients
20
21 with intellectual disabilities, and all 631 (100%) did so. Adults were also identified via
22
23 the intellectual disabilities health and social work services including day services, the
24
25 Health Board register, and records of financial payments for any service by social work.
26
27 This process led initially to an over-identification, such as people with IQ scores in the
28
29 70-80 range with additional complex health needs. All were systematically reviewed by
30
31 nurses in the intellectual disabilities health service, and this group were removed. Thus,
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33 a register was compiled, and subsequently updated annually via general practices, with
34
35 central support from the intellectual disabilities health service, until 2017 when services
36
37 were redesigned. The identified adult prevalence of intellectual disabilities within the
38
39 area was 3.33 per 1,000 in 2000-2001.
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44 **Process and data collection**

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46 With initial piloting in 2001, each participant had a detailed assessment of their general
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48 and mental health, and demographic factors, completed 2002-2004. One of six specially
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50 trained, registered nurses reviewed each person's primary health care records, then
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52 used a semi-structured tool, the C21st Health Check, to assess clinical factors and the
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54 level and cause of intellectual disabilities. In addition to a review of existing health
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56 problems and all bodily health systems, a physical examination was undertaken,
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58 including assessment of vision and hearing, measurement of height and weight, and a
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60 phlebotomy protocol followed. All information was then reviewed by the nurse with one

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3 of three general practitioners with a special interest in intellectual disabilities, and any
4 further investigations that were indicated were completed. Previously known, and newly
5 identified, conditions were then classified using the *International Statistical Classification*
6 *of Diseases and Related Health Problems, 10th Revision (ICD-10)*.²² Anyone identified to
7 have possible, probable, or definite mental ill-health, autism, or problem behaviours was
8 then fully assessed by the project's intellectual disabilities psychiatrists. Each person's
9 assessment findings were then case conferenced by the two Consultant psychiatrists,
10 and diagnoses were derived and agreed according to clinical diagnoses, *ICD-10*
11 *(Diagnostic Criteria for Research)*,²³ *Diagnostic and Statistical Manual of Mental*
12 *Disorders-IV-TR*,²⁴ and *Diagnostic Criteria for Psychiatric Disorders for use with Adults*
13 *with Learning Disabilities (DC-LD)*.²⁵ Information was also collected on demographics,
14 and community, hospital, and social service use. Further details are provided
15 elsewhere.^{26,27} The data were entered into a database by two dedicated data-entry staff.

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31 Each person in Scotland is given a number unique to them at birth or first registration
32 with a general practitioner, which is used in almost all subsequent health service
33 encounters, and on certification of death. The numbers are held on the Community
34 Health Index (CHI) database at National Services Scotland. These CHI numbers provided
35 a means to record link each participant with National Records for Scotland death
36 certification data. This linkage was performed in 2018, and the linked data were held in
37 the NHS Greater Glasgow & Clyde (NHS GG&C) Safe Haven. Data on immediate,
38 underlying, and contributory causes of deaths by ICD-10 codes, age at death, and place
39 of death were extracted.

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51 In order to provide finer granularity of cause of death, two clinical academics then
52 grouped specific causes of death into narrower groupings than those provided by ICD-10
53 chapter headings (supplementary table 2). This approach was also in view of the
54 recognised issue of variation between health staff in distinguishing and recording
55 immediate causes of death, and because some causes occurred in low numbers so could

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3 not be individually reported due to the risk of statistical disclosure. Additionally, some
4 conditions likely to be the same are spilt between different ICD-10 chapters, e.g.
5 dementia in Alzheimer disease (F00) and unspecified dementia (F03) in the ICD-10
6 mental and behavioural disorders chapter, and Alzheimer's disease (G30) and
7 Alzheimer's disease, unspecified (G30.9) in the ICD-10 diseases of the nervous system
8 chapter. A list of related conditions was generated by one of the clinical academics and
9 then checked by the second.
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19 - Supplementary table 2 -
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23 **Analyses**

24 All statistical analyses were conducted using R for Windows v3.3.0 or SAS 9.3 (SAS
25 Institute, Cary NC) and were performed within the NHS GG&C Safe Haven environment.
26 Due to disclosure principles of the Safe Haven, results with counts of less than 5 cannot
27 be released; these have been referred to as <5 throughout. Similarly, if it is deemed
28 possible that participants may be identified from the results, these may be omitted.
29 Details are provided if this occurred.
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40 Data were summarised for the population of adults aged 16+ years with intellectual
41 disabilities. Categorical variables were summarised with the number and percentages of
42 people falling into each category and the number of missing data. Continuous variables
43 were summarised with the number of observations and those missing, the mean and
44 standard deviation (SD), and the minimum and maximum values, unless otherwise
45 stated.
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54 Participant characteristics were summarised overall and for those alive and those
55 deceased. For those who are deceased, their data including age at death,
56 underlying/contributing causes of death, and location of death were summarised for
57 those with and without Down syndrome. Location codes for place of death are provided
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3 where available. We assumed those with the code for non-institutional location to have
4 died at home. Due to small numbers, location codes have been grouped together for
5 NHS hospitals, home, and other hospitals/care facilities including hospices.
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11 Mortality incidence rates have been calculated using the number of deaths in the cohort
12 divided by the number of person years alive within the study period multiplied by
13 100,000, overall and for those with and without Down syndrome. SMRs were calculated
14 using population data for those aged 15 and over within NHS GG&C in 2010.^{28,29} Death
15 rates for males and females by 5 year band ages groups spanning from 15-20 years old
16 to 90 years and over were summed to form the expected death rates for the general
17 population. The observed death rate for adults with intellectual disabilities was taken
18 from our study results. The observed/expected death rates were calculated for the
19 intellectual disabilities cohort overall then separately by age group, sex, ability level, and
20 for the adults with, and without, Down syndrome, and ICD-10 chapter for cause of
21 death, and compared to the general population.
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36 Deaths were also analysed for those that could be considered as deaths that would have
37 been avoidable. The Office for National Statistics (ONS) published a definition of
38 avoidable mortality,³⁰ which lists the causes of amenable deaths (deaths that should not
39 occur in the presence of good health care, e.g. respiratory disease), and causes of
40 preventable deaths (e.g. from diseases that could have been avoided by prior
41 immunisation), by ICD-10 codes. Causes of death for the adults with intellectual
42 disabilities have been summarised by ONS definition of avoidable deaths.
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51 To determine the demographic and clinical factors associated with death in adults with
52 intellectual disabilities, time to event analyses were explored using univariate Cox
53 Proportional Hazards models. Variables were selected as potentially relevant on the basis
54 of what is known on causes of death in people with intellectual disabilities, the 20 most
55 common physical health conditions reported in the adult population with intellectual
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3 disabilities,²¹ and other factors hypothesised as potentially clinically relevant

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5 (supplementary table 3):

- 6
7 • Demographics - 9 variables.
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9 • Clinical conditions - 33 variables.
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11 • Service use - 3 variables.
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13 • Prescriptions - 5 variables.
14

15 All 50 variables were then permitted entry in to a single multivariable analysis using
16 stepwise regression methods, in order to identify a model containing the statistically
17 significant factors associated with death. Age at date of the health assessment was
18 entered in to the model as a continuous measure. Results from the univariate Cox
19 Proportional Hazards models (Supplementary table 3) and the statistically significant
20 multivariable model from the stepwise results have been presented with hazard ratios
21 with corresponding 95% confidence intervals (HR, 95% CI) and p-values were obtained.
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31 - Supplementary table 3 -
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34 35 ***Patient and public involvement***

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37 This study was designed to respond to the growing concern expressed by people with
38 intellectual disabilities, their families, and third sector organisations about the early
39 deaths of people with intellectual disabilities. The Scottish Learning Disabilities
40 Observatory, where this research was undertaken, has a specific remit for people with
41 intellectual disabilities. Its steering group includes partners from third sector
42 organisations, including Down syndrome Scotland, and people with intellectual
43 disabilities, who approved the work plan for this project prior to it commencing. Results
44 from this study will be disseminated for people with intellectual disabilities in an easy-
45 read version via the Scottish Learning Disabilities Observatory.
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58 **Results**

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Population characteristics

962 of the original 1,023 (94.0%) adults with intellectual disabilities who were assessed were linked to a CHI number enabling the extraction of relevant death data. Reasons for the unlinked 61 people could be due to moving out of the area, or a recording mistake. 1 further participant was removed from the analysis due to inaccurate recording of dates, leaving 961 adults in the cohort (93.9%). Of these 961 adults, 294 (30.6%) had a record of death. Table 1 shows the baseline characteristics of the full cohort of 961, the adults who died, and those still alive at the time of linkage.

- Insert table 1 about here -

Age at death, and mortality incidence

The mean age at death was 61.0 years (SD=7.0 years). Of the 961 adults, 64 (35.8%) of the 179 adults with Down syndrome, and 230 (29.4%) of the 782 adults without Down syndrome had a record of death. Their mean age of death was 56.9 years (SD=4.3 years) for the adults with Down syndrome, and 62.2 years (SD=7.5 years) for the adults without Down syndrome. Mortality incidence for the cohort during the study period was 3,049.0 per 100,000 person years follow-up, with 3,832.1 per 100,000 for those with Down Syndrome and 2,885.0 for those without Down syndrome.

Standardised mortality ratios

Compared with the general population, the SMR was 2.24 (1.98, 2.49) overall; 5.28 (3.98, 6.57) for adults with Down syndrome, 1.93 (1.68, 2.18) for adults without Down syndrome; 1.69 (1.42, 1.95) for men and 3.48 (2.90, 4.06) for women. SMRs were higher the more severe the level of intellectual disabilities, with people with profound intellectual disabilities having an SMR of 4.14 (3.11, 5.17). SMR was high for all age groups (though for the 15-25 year age group, the wide confidence interval includes one, perhaps due to the smaller number of deaths in this group); this decreased as age increased. SMRs were high for most ICD-10 chapter groups of conditions, particularly so

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3 for congenital malformations at 17.26 (10.75, 23.78), diseases of the digestive system
4 at 16.13 (8.23, 24.04), mental and behavioural disorders at 12.64 (3.27, 22.00), and
5 external causes at 11.08 (3.40, 18.76). Details are shown in table 2.
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11 - Insert table 2 about here -
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14 15 **Causes of death**

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17 Cause of death data was available from death certificates for 262 (89.1%) of 294
18 participants who had died, which include 57 (89.1%) participants with Down syndrome,
19 and 205 (88.7%) participants without Down syndrome. Table 3 shows the underlying
20 causes of death by ICD-10 chapters separately for the adults with, and without Down
21 syndrome. For the whole cohort, diseases of the respiratory system were the most
22 common (21.8%), then diseases of the circulatory system (19.1%), then diseases of the
23 nervous system (13.0%), and neoplasms, followed by congenital anomalies (10.3%).
24 For the adults with Down syndrome, congenital anomalies were the most common (in all
25 cases this was a record of "Down syndrome"), then jointly diseases of the respiratory
26 system and diseases of the circulatory system, then diseases of the nervous system,
27 followed by infections, and mental and behavioural disorders. For the adults without
28 Down syndrome, diseases of the respiratory system were the most common, then
29 diseases of the circulatory system, then neoplasms, then diseases of the nervous
30 system, followed by diseases of the digestive system. Table 4 presents the most
31 common underlying causes of death by individual causes, or related groups of causes,
32 with finer granularity than ICD-10 chapter headings (groups are shown in supplementary
33 table 2). Causes are listed in the order of how common they were in the whole cohort.
34 Data are presented separately for the adults with, and without Down syndrome. For the
35 whole cohort, the most common cause was aspiration/reflux/choking, then respiratory
36 infection, then other malignancy (non gastrointestinal), then other condition (mostly
37 unrelated conditions that could not be reported individually or as groups, due to
38 individually occurring at a frequency of <5). For the adults with Down syndrome, Down
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3 syndrome was the most common cause, then dementia, then other infection. For the
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5 adults without Down syndrome, aspiration/reflux/choking was the most common cause,
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7 then respiratory infection, then other malignancy (non gastrointestinal). For the 21
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9 people whose death certificate listed Down syndrome as their underlying cause of death,
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11 the death certificates were reviewed and underlying cause of death reclassified, as a
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13 sensitivity check. Following this, the most common underlying causes of death for the
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15 adults with Down syndrome were dementia (n=20; 35.1%), then other infection (n=7;
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17 12.3%).

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21 - Insert tables 3 and 4 about here -
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25 Table 5 shows the all contributing causes of death data, again presenting the most
26
27 common causes by individual causes, or related groups of causes with finer granularity
28
29 than ICD-10 chapter headings. Data is presented separately for the adults with, and
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31 without Down syndrome. For the whole cohort, respiratory infection was the most
32
33 common cause (27.1%), followed by aspiration/reflux/choking (19.8%), other conditions
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35 (15.6%), other cardiovascular conditions (non acute myocardial nor other ischaemic
36
37 heart disease: 14.5%), then other respiratory conditions. For the adults with Down
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39 syndrome, Down syndrome was the most common, then dementia, then respiratory
40
41 infection, then aspiration/reflux/choking. For the adults without Down syndrome,
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43 respiratory infection was the most common cause, then aspiration/reflux/choking, then
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45 other condition, then other respiratory conditions, and intellectual disabilities.
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49 - Insert table 5 about here -
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51 52 53 **Avoidable deaths**

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55 According to the ONS list of avoidable deaths, 102 (38.9%) of the 262 deaths were
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57 avoidable; most notably, respiratory infection and epilepsies (table 4). 78 (29.8%) were
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59 deaths that are amenable to good health care, whilst 51 (19.5%) were preventable
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3 deaths. 27 (10.3%) deaths were classed as both amenable and preventable deaths. This
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5 compares to published Scottish death data showing in 2018 that 28% of deaths were
6
7 avoidable; 14% amenable and 24% preventable, similar to the figures in the previous
8
9 four years (data not available prior to 2014).³¹ For the 57 deaths of adults with Down
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11 syndrome, 17 (29.8%) deaths were avoidable, 15 (26.3%) deaths were amenable to
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13 good health care, whilst 7 (12.3%) were preventable. 5 (8.8%) were both amenable and
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15 preventable. For the 205 deaths of adults without Down syndrome, 85 (41.5%) were
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17 avoidable, 63 (30.7%) deaths were amenable to good health care, whilst 44 (21.5%)
18
19 were preventable. 22 (10.7%) were both amenable and preventable.
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23 ***Place of death***

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25 Of the 262 participants for whom place of death was known, 158 (60.3%) died in an
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27 NHS Hospital, 70 (26.7%) died at home, and 34 (13.0%) died within other
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29 hospitals/care facilities. This was similar for both the adults with Down syndrome: 31
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31 (54.4%) in an NHS hospital, 17 (29.8%) at home, and 9 (15.8%) within other
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33 hospitals/care facilities; and the adults without Down syndrome: 127 (62.0%) in an NHS
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35 hospital, 53 (25.9%) at home, and 25 (12.2%) within other hospitals/care facilities.
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39 ***Factors associated with risk of death***

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41 The results from the univariate cox proportional hazards models indicated that of the
42
43 original 50 potential variables, factors associated with risk of death were (supplementary
44
45 table 3):
46

- 47 • Demographics – age at the time of the health assessment, more severe learning
48 disabilities, accommodation type (not living with family carer), not having day-time
49 occupation, and being a smoker (but not sex, the extent of neighbourhood
50 deprivation, civil status, nor Down syndrome, in view of the confidence intervals).
- 51 • Clinical conditions – having spastic quadriplegia, hearing impairment, visual
52 impairment, diabetes, percutaneous endoscopic gastrostomy/tube fed, constipation,
53 ataxia/gait disorder, osteoporosis, hypertension, dysphagia, dyspnoea, gastro-
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oesophageal reflux disorder, lower respiratory tract infection, total number of physical health disorders, not having impaired mobility, not having urinary incontinence, not having bowel incontinence, and not having autism (but not epilepsy, body mass index, nail disorder, epidermal thickening, cerebral palsy, fungal infection, musculoskeletal pain, bone deformity, dental/oral problem, eczema/dermatitis, psychosis, affective disorder including bipolar affective disorder, problem behaviour, eating disorder including pica, nor any mental illness).

- Service use – number of general practitioner consultations in the previous 12 months, total number of different types of health professionals providing care at the time of the clinical assessment, (but not number of accident and emergency attendances in the previous 12 months).
- Prescriptions – antiepileptic drugs, total number of different types of drugs, (but not antipsychotic drugs, antidepressant drugs, nor anxiolytic drugs).

Table 6 shows the final model of the variables retained in the multivariable analysis for time to death. The significant factors indicating an increased risk of death were increased age at the time of the health assessment, smoking, Down syndrome, diabetes, being percutaneous endoscopic gastrostomy/tube fed, lower respiratory tract infection at cohort inception, epilepsy, hearing impairment, and total number of different types of drugs prescribed, whilst bowel incontinence showed a reduced risk of death. Of note, level of intellectual disabilities whilst significant in the univariate analysis, was not retained in the multivariable model.

- Insert table 6 about here -

Discussion

Principle findings and interpretation

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3 As far as we are aware, this is the first population-based study of adults with intellectual
4 disabilities to report in detail the factors associated with time to death, and to describe
5 their causes of death and quantify the SMR separately for adults with Down syndrome
6 and adults without Down syndrome. This is important, since adults with Down syndrome
7 form a notable proportion of all adults with intellectual disabilities (19% in this cohort),
8 and because they have a different pattern of clinical conditions compared with other
9 adults with intellectual disabilities.²¹ We found that aspiration/reflux/choking is the most
10 common underlying cause of death in adults with intellectual disabilities, followed by
11 respiratory infection. They are also the most common all contributing causes of death.
12 The profile differed in the adults with Down syndrome for whom "Down syndrome",
13 followed by dementia, were recorded as the most common underlying cause of death,
14 and all contributing causes of death (or alternatively, dementia, then other infection
15 were the most common underlying causes when "Down syndrome" deaths were
16 reclassified); with the next most common all contributing cause of death being
17 respiratory infection, then aspiration/reflux/choking. The proportion of deaths that would
18 have been amenable to good care for adults with intellectual disabilities was more than
19 double that seen in the general population. Although aspiration/reflux/choking is not
20 included in the ONS list of avoidable deaths, and therefore not included in the figures we
21 report on amenable deaths, we consider that good care could have prevented many of
22 these deaths. This appears to be very important for adults with intellectual disabilities
23 irrespective of whether they have Down syndrome. Similarly, some other causes of
24 deaths within this cohort (supplementary table 2), such as constipation/mega-colon, and
25 urinary tract infections do not appear on the ONS list of avoidable deaths.

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52 Clearly, this pattern of causes of death differs from that seen in the general population,
53 in whom the most common underlying causes of death are heart disease, then dementia,
54 then lung cancer in men, and dementia, then heart disease, then stroke in women.³²
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3 reporting 0% for adults with Down syndrome, and 15.2% for adults with intellectual
4 disabilities without Down syndrome – presumably as the adults with intellectual
5 disabilities are dying younger from other causes, and cancers increase with age.
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11 We found an overall SMR of 2.24; 5.28 in the adults with Down syndrome and 1.93 for
12 the adults without Down syndrome. SMRs were higher for most ICD-10 chapter
13 groupings of conditions. It was higher in the women than the men, as has been
14 previously reported in most (supplementary table 1), but not all^{10,19} previous reports.
15 The reason for this is unknown; in the general population, mortality rates have fallen in
16 recent decades, and more so in middle and older aged men than women (i.e. the sex
17 gap is narrowing at these ages), but we do not know what trends over time there have
18 been for people with intellectual disabilities. Having intellectual disabilities removes
19 differences in lifespan by sex compared with the general population; but sex was not a
20 predictor of mortality in our study, so the SMR difference may only be because of the
21 difference found in the general population by sex. SMRs were lowest with older age
22 groups, likely to be due to increased illness in the older general population and
23 conversely a healthier group with intellectual disabilities living to older ages compared
24 with those who die younger (as has previously been reported³³). Although SMR was
25 higher with increasing severity of intellectual disabilities, ability level was not retained
26 within the multivariable model on time to death. The factors that were independently
27 associated with increased risk of death, in order, were being percutaneous endoscopic
28 gastrostomy/tube fed, Down syndrome, diabetes, having a lower respiratory tract
29 infection at entry to the cohort, smoking, epilepsy, hearing impairment, total number of
30 prescribed drugs, and age, whilst bowel incontinence had a reduced risk of death. Some
31 of these predictors are similar to those reported in the general population, suggesting
32 earlier mortality of adults with intellectual disabilities is largely accounted for by the
33 higher rates of multi-morbidities that they experience compared with other people, and
34 amenable deaths.³⁴
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3 Whilst accommodation type (not living with a family carer), ability level, not having day-
4 time occupation, having spastic quadriplegia, visual impairment, constipation, ataxia/gait
5 disorder, osteoporosis, hypertension, dysphagia, dyspnoea, gastro-oesophageal reflux
6 disorder, total number of physical health disorders, not having impaired mobility, not
7 having urinary incontinence, and not having autism, number of general practitioner
8 consultations in the previous 12 months, total number of different types of health
9 professionals providing care at the time of the health assessment, and antiepileptic
10 drugs were related to time of death on univariate analyses, they were not retained in the
11 multivariable model.
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23 The majority of the adults with intellectual disabilities, with and without Down syndrome,
24 died in an NHS hospital.
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29 ***Comparison with previous literature***

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31 The overall SMR we report, higher SMR in women than men, and higher SMR at younger
32 age groups is similar to the majority of previous reports. Most mortality studies with
33 people with Down syndrome have been conducted with children. Previous reports of
34 children and adults (combined) gave an SMR=5.5,²⁰ and for adults SMR=7.6,⁹ compared
35 with our finding for adults with Down syndrome of SMR=5.28. Recent systematic reviews
36 reported people with intellectual disabilities on average died 20 years younger than other
37 people, and people with Down syndrome died 28 years younger, although the majority
38 of the Down syndrome studies were not recent.^{1,2} In our study we found the gap
39 between the age at death of people with intellectual disabilities with and without Down
40 syndrome to be only 5.3 years, possibly reflecting the increasing lifespan of people with
41 Down syndrome exceeding increases in lifespan for people with intellectual disabilities
42 without Down syndrome. Notably, after "Down syndrome", dementia was the most
43 commonly reported underlying, and all contributing cause of death for the adults with
44 Down syndrome, whereas studies in the past commented on congenital heart disease
45 and respiratory causes.
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5 For the cohort overall, respiratory infection and aspiration/reflux/choking were the most
6 common all contributing causes of death. These conditions feature in previous studies on
7 causes of death,^{5,6,8,10,11} although there are inconsistencies between studies. By ICD-10
8 chapter, our study found the most common underlying causes of death were diseases of
9 the respiratory system, then of the circulatory system, followed by neoplasms. Others
10 reported the most common to be vascular,¹⁰ circulatory,⁵ heart disease,¹⁷ and jointly
11 circulatory and neoplasm.¹⁹
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21 Previous research from other countries has highlighted that listing Down syndrome or
22 intellectual disabilities as the underlying cause of death obscures actual causes of death
23 for this population.³⁵ We therefore presented data on revised cause of death for the 21
24 people for whom it was listed as Down syndrome (as a sensitivity check), and highlight
25 with interest that in this Scottish cohort no-one had intellectual disabilities listed as
26 underlying cause of death. This may reflect different medical death certificate recording
27 practices in Scotland compared to e.g. USA.
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38 Studies that investigated avoidable deaths in adults with intellectual disabilities found
39 them to be more common than in the general population, due to deaths that would have
40 been amenable to good care. Avoidable deaths have been reported in 44.7% of deaths
41 of people with intellectual disabilities in England (mostly amenable deaths – figure not
42 reported),⁶ and in 31% in Australia,¹⁹ compared with our figure of 38.9%. Avoidable
43 deaths that would have been amenable to good care have been reported to occur in 37%
44 of deaths of people with intellectual disabilities in England.⁵ Our figure is slightly lower at
45 29.8% but still more than double that found in the Scottish general population.³¹ It
46 should be noted that the ONS list of avoidable deaths was not designed specifically for
47 people with intellectual disabilities, and it may emphasise some causes less relevant, and
48 omit others that might be highly relevant in this population.⁵
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Strengths and limitations

The strengths of the study include the thorough methods of case ascertainment for intellectual disabilities at baseline with verification of intellectual disabilities and its severity, suggesting results are generalisable in other high income countries. Whilst our Identification of the population will not have identified everyone with intellectual impairment (an IQ<70), in view of the multiple sources used, we believe it will have identified the adults with intellectual disabilities (IQ<70, plus need for support in daily activities, and onset in the developmental period). Additionally, there were detailed clinical assessments at baseline, and a longitudinal design. The size of the cohort and the duration of follow-up is also a strength, as is the successful record linkage for 94% of participants. Our study does have limitations, specifically that the study was only conducted in one region of Scotland, and the reliance upon death certificate data to obtain cause of death. Additionally, the characteristics and health of the participants was collected in 2002-2004. The health conditions we investigated tend to be long-standing or remitting/relapsing conditions, and psychotropic prescribing also once initiated tends to be long-standing in people with intellectual disabilities. However, it is possible that extent of neighbourhood deprivation, type of accommodation, employment, and civil status (though few marry) might have changed for some people between 2002-2004 and 2018; we have no further information to check this. There were no concerns regarding the proportional hazards assumption in the multivariable model. The linkage was also reliant on the accuracy of the CHI number as a sole source of linkage.

Implications

It is important to know the factors that are associated with risk of death, and the common causes of death in this population, as these then inform the actions needed to reduce the unacceptably high SMRs experienced by people with intellectual disabilities. Awareness of these factors may provide a pathway to action to reduce the observed earlier mortality in adults with intellectual disabilities. It is not adequate to solely rely on the public health interventions available to everyone, even when they are accessible.

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3 Aspiration, reflux, and choking could, and should, be avoided by raising awareness of its
4 consequences (death), and putting in place training on simple measures related to
5 feeding, positioning, food consistency, and when to seek health advice from speech and
6 language therapy, physiotherapy, nursing, and medical advice. Carers need to be aware
7 of how the adults they care for express pain, so that conditions such as gastrointestinal
8 ulcers are attended to, prior to the extreme point of perforation, and so treatable
9 conditions such as constipation and urinary tract infections are managed before they
10 lead to respiratory distress and sepsis. Quality of care is important; adults with
11 intellectual disabilities need just as good care for their diabetes and epilepsy (and other
12 conditions) as the rest of the population, with reasonable adjustments to address
13 accessibility, and accessible smoking cessation programs.
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28 **Future research**

29 Further research on larger samples is needed, particularly with regards to replicating and
30 extending our findings on the factors that are associated with risk of death, and any sex
31 differences in them, so that practitioners can focus on actions to improve the life
32 expectancy of adults with intellectual disabilities, with and without Down syndrome.
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48 **Competing interests**

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52 The authors declare no competing interests.
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56 **Author's contributions**

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3 S-AC is principle investigator, she conceived and managed the project, interpreted data,
4 and wrote the first draft of the manuscript. LA contributed to the conception of the
5 project, and project management. NG designed and supervised the statistical analysis,
6 and contributed to data interpretation and drafting of the manuscript. PMcS implemented
7 and refined the statistical analysis, and contributed to data interpretation, and drafting of
8 the manuscript. AJ implemented and refined the statistical analysis, and contributed to
9 data interpretation. AH contributed to data linkage and interpretation, and drafting of the
10 manuscript. CMcC provided expertise on data linkage and methods, and drafting of the
11 manuscript. DK contributed to data interpretation and drafting of the manuscript. CM
12 contributed to data interpretation, and drafting of the manuscript. All approved the final
13 version of the manuscript. S-AC is the study guarantor.
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28 **Data sharing**

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31 Data is available via NHS GG&C Safe Haven upon application.
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40 team for their contribution to the study, and the participants with intellectual disabilities
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Table 1. Cohort characteristics at time of the health assessment, summarised overall and by death status during the follow-up period

Variable	Statistics / Groups	All participants (N=961)	Deceased participants (N=294)	Alive participants (N=667)
Age (years)	Mean (SD)	44.1 (14.6)	52.4 (13.6)	40.5 (13.6)
	Min, max	16, 83	18, 83	16, 77
Age group	16-25 years	127 (13.2%)	10 (3.4%)	117 (17.5%)
	26-35 years	153 (15.9%)	26 (8.8%)	127 (19.0%)
	36-45 years	246 (25.6%)	49 (16.7%)	197 (29.5)
	46-55 years	205 (21.3%)	85 (28.8%)	120 (18.0%)
	>55 years	230 (23.9%)	124 (42.0%)	106 (15.9%)
Sex	Male	525 (54.6%)	154 (52.4%)	371 (55.6%)
	Female	436 (45.3%)	140 (47.5%)	296 (44.4%)
Ability level	Mild ID	382 (39.7%)	92 (31.2%)	290 (43.5%)
	Moderate ID	236 (24.5%)	73 (24.7%)	163 (24.4%)
	Severe ID	180 (18.7%)	67 (22.7%)	113 (16.9%)
	Profound ID	163 (17.0%)	62 (21.1%)	101 (15.1%)
Accommodation type	Family carer	374 (38.9%)	70 (23.8%)	304 (45.6%)
	Independent	93 (9.7%)	36 (12.2%)	57 (8.5%)
	Paid support	435 (45.2%)	161 (54.6%)	274 (41.1%)
	Congregate care	59 (6.1%)	27 (9.2%)	32 (4.8%)
Down syndrome	No	782 (81.4%)	230 (78.2%)	552 (82.8%)
	Yes	179 (18.6%)	64 (21.7%)	115 (17.2%)

ID=intellectual disabilities; SD=standard deviation

Table 2. Standardised mortality ratios

Variable	Groups	SMR (95% CI)
All participants	-	2.24 (1.99, 2.50)
Age group*	15-25 years	18.73 (0.37, 37.09)
	26-35 years	4.21 (1.29, 7.13)
	36-45 years	3.86 (2.28, 5.44)
	46-55 years	3.77 (2.90, 4.74)
	>55 years	1.86 (1.60, 2.12)
Sex	Male	1.69 (1.42, 1.95)
	Female	3.48 (2.90, 4.06)
Ability level	Mild ID	1.60 (1.27, 1.92)
	Moderate ID	2.10 (1.62, 2.58)
	Severe ID	2.78 (2.11, 3.44)
	Profound ID	4.14 (3.11, 5.17)
Down syndrome	No	1.93 (1.68, 2.18)
	Yes	5.28 (3.98, 6.57)
Underlying causes of death grouped by ICD-10 chapter**	Congenital malformations, deformations and chromosomal abnormalities	17.26 (10.75, 23.78)
	Diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism	7.50 (-7.20, 22.20)
	Diseases of the circulatory system	5.55 (4.01, 7.09)
	Diseases of the digestive system	16.13 (8.23, 24.04)
	Diseases of the genitourinary system	3.65 (0.73, 6.57)
	Diseases of the musculoskeletal system and connective tissue	5.40 (-0.71, 11.52)
	Diseases of the nervous system	7.73 (5.13, 10.32)
	Diseases of the respiratory system	6.78 (5.02, 8.54)

	Diseases of the skin and subcutaneous tissue	2.75 (-2.64, 8.15)
	Endocrine, nutritional and metabolic diseases	3.43 (1.05, 5.81)
	External causes of morbidity and mobility	11.08 (3.40, 18.76)
	Infectious and parasitic diseases	8.93 (1.78, 16.07)
	Mental and behavioural disorders	12.64 (3.27, 22.00)
	Neoplasms	6.31 (4.19, 8.43)
	Symptoms, signs and abnormal clinical and laboratory findings, not elsewhere classified	19.51 (0.39, 38.63)

CI=confidence intervals; ID=intellectual disabilities; SMR=standardised mortality ratios

*Data used for comparison with General Population (GG&C Health Board) provides data in 5 year age bands therefore 15+. Data on adults with ID are 16+

** Negative Lower CI and wide CIs indicate low number of observed deaths in study population

Table 3. Underlying causes of death grouped by ICD-10 chapter, where cause of death is known

ICD-10 chapter	Participants with Down syndrome (N=57)	Participants without Down syndrome (N=205)
Certain infectious and parasitic diseases	5 (8.8%)	<5
Neoplasms	<5	33 (16.1%)
Diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism	<5	<5
Endocrine, nutritional and metabolic diseases	<5	8 (3.9%)
Mental and behavioural disorders	5 (8.8%)	<5
Diseases of the nervous system	7 (12.3%)	27 (13.2%)
Diseases of the eye and adnexa	<5	<5
Diseases of the ear and mastoid process	<5	<5
Diseases of the circulatory system	8 (14.0%)	42 (20.5%)
Diseases of the respiratory system	8 (14.0%)	49 (23.9%)
Diseases of the digestive system	<5	16 (7.8%)
Diseases of the skin and subcutaneous tissue	<5	<5
Diseases of the musculoskeletal system and connective tissue	<5	<5
Diseases of the genitourinary system	<5	5 (2.4%)
Pregnancy, childbirth and the puerperium	<5	<5
Certain conditions originating in the perinatal period	<5	<5
Congenital malformations, deformations and chromosomal abnormalities	21 (36.8%)	6 (2.9%)
Symptoms, signs and abnormal clinical and laboratory findings, not elsewhere classified	<5	<5
External causes of morbidity and mortality	<5	7 (3.4%)
All deaths	57 (100%)	205 (100%)

ICD-10=International Statistical Classification of Diseases and Related Health Problems, 10th Revision

Table 4. Underlying causes of death grouped by specific individual causes or related groups of causes, where cause of death is known

Causes	Participants with Down syndrome (N=57)	Participants without Down syndrome (N=205)
Aspiration/reflux/choking	<5	22 (10.8%)
Respiratory infection	<5	21 (10.3%)
Down syndrome	21 (36.8%)	<5
Other malignancy	<5	19 (9.3%)
Other condition	<5	17 (8.3%)
Epilepsies	<5	13 (6.4%)
Acute myocardial infarction	<5	13 (6.4%)
Gastro-intestinal malignancy	<5	12 (5.9%)
Stroke	<5	11 (5.4%)
Other cardiovascular disease	<5	11 (5.4%)
Other respiratory condition	<5	9 (4.4%)
Other infection	5 (8.8%)	6 (2.9%)
Cerebral palsy	<5	11 (5.4%)
Dementia	9 (15.8%)	<5
Other gastrointestinal disorders	<5	8 (3.9%)
Ulcer/gastrointestinal perforation	<5	7 (3.4%)
Diabetes	<5	7 (3.4%)
Other congenital condition	<5	6 (2.9%)
Other ischaemic heart condition	<5	6 (2.9)
Mental health	<5	<5
Other neurological conditions	<5	<5
Renal failure	<5	<5
All deaths	57 (100%)	205 (100%)

Table 5. All contributing causes of death grouped by specific individual causes or related groups of causes, where cause of death is known

Causes	Participants with Down syndrome (N=57)	Participants without Down syndrome (N=205)
Respiratory infection	22 (38.6%)	49 (23.9%)
Aspiration/reflux/choking	11 (19.3%)	41 (20.0%)
Down syndrome	43 (75.4%)	<5
Other condition	8 (14.0%)	33 (16.1%)
Other cardiovascular disease	8 (14.0%)	30 (14.6%)
Other respiratory conditions	<5	31 (15.1%)
Other infection	9 (15.8%)	24 (11.7%)
Intellectual disabilities	<5	31 (15.1%)
Epilepsies	8 (14.0%)	24 (11.7%)
Dementia	24 (42.1%)	<5
Other neoplasms	<5	23 (11.2%)
Cerebral palsy	<5	24 (11.7%)
Acute myocardial infarction	5 (8.8%)	19 (9.3%)
Other gastrointestinal disorders	<5	18 (8.8%)
Diabetes	<5	19 (9.3%)
Other ischaemic heart disease	<5	19 (9.3%)
Renal failure	<5	16 (7.8%)
Stroke	<5	17 (8.3%)
Other congenital condition	<5	15 (7.3%)
Gastrointestinal malignant neoplasm	<5	12 (5.9%)
Ulcer/gastrointestinal perforation	<5	10 (4.9%)
Mental health	<5	10 (4.9%)
Other neurological condition	<5	8 (3.9%)
Heart failure	<5	7 (3.4%)
Injuries and accidents	<5	8 (3.9%)
Medical/surgical complications	<5	<5
Secondary malignancies	<5	<5
Thyroid disorders	<5	<5
Metabolic disorder	<5	<5
All deaths	57 (100%)	205 (100%)

Table 6. Multivariable model results for the outcome time to death

Variable		Hazard ratio	95% CI	p-value
Age at time of health assessment		1.056	1.046, 1.066	<0.0001
Smoker	No	1	-	
	Yes	1.531	1.1011, 2.128	0.0112
Down syndrome	No	1	-	
	Yes	2.440	1.787, 3.332	<0.0001
Epilepsy	No	1	-	
	Yes	1.511	1.173, 1.946	0.0014
Hearing impairment	No	1	-	
	Yes	1.320	1.030, 1.692	0.0284
Bowel incontinence	No	1	-	
	Yes	0.490	0.376, 0.640	<0.0001
Diabetes	No	1	-	
	Yes	2.346	1.553, 3.542	<0.0001
PEG/tube fed	No	1	-	
	Yes	2.346	1.135, 5.989	0.00240
Lower respiratory track infection	No	1	-	
	Yes	1.782	1.315, 2.415	0.0002
Total number of prescribed drugs		1.066	1.016, 1.118	0.0085

CI=confidence interval; PEG=percutaneous endoscopic gastrostomy

Rates, causes, place, and predictors of mortality in adults with intellectual disabilities with and without Down syndrome: cohort study with record linkage

Supplementary table 1. Previously reported standardised mortality ratios, causes, and risks for death

Author	Country	SMR (95% confidence interval)	Number of deaths	Causes of death and risk factors for death
Forsgren et al (1996) ⁷	Sweden	4.2 (3.3, 5.3) at 20-59y; 1.1 (0.9, 1.5) at 60+y <i>Without epilepsy:</i> 3.8 (2.8, 5.0) at 20-59y; 1.1 (0.8, 1.5) at 60+y <i>With epilepsy:</i> 5.0 (2.9, 8.7) at 20-59y; 2.4 (0.9, 6.1) at 60+y <i>With epilepsy and cerebral palsy:</i> 8.0 (4.1, 15.7) at 20-59y; 0.9 (0.1, 6.6) at 60+y <i>M:</i> 1.6 (1.2, 2.0) at 0-60+y <i>F:</i> 2.6 (2.0, 3.3) at 0-60+y <i>Mild ID:</i> 1.8 (1.1, 2.7) at 0-60+y <i>Moderate ID:</i> 1.5 (1.1, 2.0) at 0-60+y <i>Severe ID:</i> 2.0 (1.5, 2.6) at 0-60+y <i>Profound ID:</i> 8.1 (5.6, 11.7) at 0-60+y	124 at 0-60+y; 112 at 20-60+y	<i>Underlying cause at 0-60+y:</i> Congenital anomalies: SMR=46.3 (32.9, 65.0) Nervous system: SMR=9.7 (5.5, 17.0) Mental disorder: SMR=4.0 (1.9, 8.4) Respiratory: SMR=3.3 (2.0, 5.5) Circulatory: SMR=2.1 (1.6, 2.7) Violent death: SMR=1.4 (0.6, 2.8) Neoplasm: SMR=0.9 (0.6, 1.6)
Durvasula & Beange (2002) ⁸	Australia	4.9 (3.4, 6.4) at 10-59y <i>M:</i> 4.1 (2.4, 5.9) at 10-59y <i>F:</i> 6.2 (3.3, 9.1) at 10-59y	40 at 10-59y; 31 at 20-59y	<i>Underlying cause at 10-59y:</i> Respiratory: 35% (pneumonia, aspiration) External causes: 20% Neoplasm: 17.5% Heart disease: 15% (congenital heart disease 50%) Gastrointestinal: 7.5% (ischaemic bowel, perforated peptic ulcer, post-operative peritonitis) Seizure: 5%
Tyrer et al (2007) ⁹	England	3.24 (2.93, 3.56) at 20-70+y <i>M:</i> 2.86 (2.50, 3.26) at 20-70+y <i>F:</i> 3.63 (3.12, 4.20) at 20-70+y 1.51 (1.23, 1.83) to 11.50 (8.14, 15.78) at 20-70+y <i>M:</i> 1.39 (1.03, 1.82) to 8.83 (5.60, 13.25) at 20-70+y <i>F:</i> 1.60 (1.18, 2.12) to 17.22 (9.64, 28.4) at 20-70+y <i>With Down syndrome:</i> 7.60 at 20-70+y <i>Without Down syndrome:</i> 2.70 at 20-70+y	409 at 20-70+y	Not reported
Patja et al (2008) ¹⁰	Finland	<i>M:</i> 2.2 at 20-39y, 1.0 at 40-59y, 1.0 at 60+y <i>F:</i> 1.4 at 20-39y, 1.1 at 40-49y, 1.0 at 60+y <i>Mild ID:</i> <i>M:</i> 1.6 at 20-39y, 1.0 at 40-59y, 1.0 at 60+y <i>F:</i> 1.2 at 20-39y, 1.1 at 40-49y, 1.0 at 60+y	1,046 at 20-97y	<i>Underlying cause at 2-97y:</i> Vascular: 36% (cardiac infarct 33%, cerebral infarct 33%, congenital heart disease 18%, pulmonary infarct 6%) Respiratory: 22% (pneumonia 83%, COPD 11%)

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		<p><i>Moderate ID:</i> M: 2.3 at 20-39y, 1.1 at 40-59y, 1.0 at 60+y F: 1.5 at 20-39y, 1.1 at 40-49y, 1.0 at 60+y</p> <p><i>Severe ID:</i> M: 2.6 at 20-39y, 1.2 at 40-59y, 1.0 at 60+y F: 1.6 at 20-39y, 1.0 at 40-49y, 1.0 at 60+y</p> <p><i>Profound ID:</i> M: 2.1 at 20-39y, 1.1 at 40-59y, 1.0 at 60+y F: 1.3 at 20-39y, 1.2 at 40-49y, 1.0 at 60+y</p>		<p>Neoplasm: 11% (digestive 44%, respiratory 15%, urogenital, 12%) Digestive: 7% (intestinal obstruction 25%, ulcer perforation 13%) Accidents and poisonings: 7% (commonest was fatal fracture, then drowning) Vascular, neoplasm, and accident causes were less common than sex-age-matched general population; Digestive were 2.5 times, Respiratory 2.6-5.8 times more common</p>
Tyrer & McGother (2009) ¹¹	England	<p>2.77 (2.53, 3.03) at 20+y M: 2.28 (2.02, 2.56) at 20+y F: 3.24 (2.83, 3.69) at 20+y</p>	503 at 20+y	<p><i>Underlying cause at 20+y:</i> Pneumonia: 13.1%, SMR=6.47 (5.00, 8.23) Nervous system: 13.1%, SMR=16.30 (12.61, 20.74) Other respiratory: 12.9%, SMR=4.64 (3.58, 5.91) Ischaemic heart disease: 11.5%, SMR=1.49 (1.13, 1.92) Neoplasm: 9.3% Congenital anomalies: 9.1%, SMR=85.60 (62.67, 114.18) Cerebrovascular disease: 7.8%, SMR=2.40 (1.71, 3.28)</p>
Oullette-Kuntz et al (2015) ¹²	Canada	<p>2.5 (2.1, 2.9) at 0-60+y M: 2.1 (1.7, 2.6) at 0-60+y F: 3.0 (2.4, 3.8) at 0-60+y M: 1.7 (1.3, 2.3) to 3.4 (2.3, 4.7) at 20-60+y F: 2.1 (1.4, 2.9) to 6.1 (4.1, 8.6) at 20-60+y</p>	172 at 0-60+y; 158 at 20-60+y	<p><i>Risk factors for death:</i> Age, Down syndrome (OR=1.76 at 20-39y; OR=1.69 at 40-59y; OR=22.34 at 60+y), cerebral palsy (OR=2.39 at 20-39y; OR=0.93 at 40-59y; OR=0.50 at 60+y), blindness/low vision (OR not given), technological dependence/medical fragility (OR=11.96 at 20-39y; OR=7.28 at 40-59y; OR=3.42 at 60+y), wheelchair dependence (OR=5.96 at 20-39y; OR=2.89 at 40-59y; OR=2.56 at 60+y), mobility impairment without wheelchair dependence (OR not given), epilepsy (OR=1.83 at 20-39y; OR=1.80 at 40-59y; OR=1.09 at 60+y)</p>
Florio & Troller (2015) ¹³	Australia	<p>2.48 (2.32, 2.64) at 0-85+y 3.15 (2.94, 3.38) at 5-69y M: 2.52 (2.29, 2.77) at 5-69y F: 4.26 (3.83, 4.74) at 5-69y</p>	953 at 0-85+y; 831 at 15+y	Not reported
McCarron et al (2015) ¹⁴	Republic of Ireland	<p>3.85 (3.70, 4.00) at 0-80+y M: 3.09 (2.93, 3.25) at 0-80+y F: 4.90 (4.63, 5.17) at 0-80+y 2.71 (2.41, 3.04) to 6.09 (5.29, 6.96) at 20-80y M: 2.50 (2.18, 2.86) to 4.50 (3.69, 5.44) at 20-80y F: 2.71 (2.32, 3.14) to 10.07 (8.99, 13.10) at 20-80y</p>	2,666 at 0-80+y; 2,394 at 20-80+y	Not reported

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1 2 3 4	Heslop & Glover (2015) ¹⁵	England	Median 2.13 (interquartile range 1.09, 2.83) across geographic areas at 18-65+y	18-65+y	Not reported
5 6 7 8 9 10 11	Lauer & McCallion (2015) ¹⁶	USA	<i>Intellectual and developmental disabilities*:</i> 1.19 at all ages, 2011 1.49 at 18+y, 2009	120,913 in 2009 at 18+y, 140,104 in 2011 at all ages	Not reported
12 13 14 15 16 17 18 19 20 21	Arvio et al (2016) ¹⁷	Finland	<i>Mild ID:</i> 2.28 (2.18, 2.39) at 0-60+y 1.99 (1.85, 2.13) to 2.77 (2.36, 3.23) at 15-60+y <i>M:</i> 2.01 (1.88, 2.14) at 0-60+y <i>F:</i> 2.80 (2.60, 3.01) at 0-60+y <i>Severe ID:</i> 3.41 (3.30, 3.52) at 0-60+y 2.07 (1.96, 2.19) to 8.77 (7.77, 9.87) at 15-60+y <i>M:</i> 2.59 (2.48, 2.72) at 0-60+y <i>F:</i> 5.24 (4.99, 5.50) at 0-60+y	5,171 at 0-60+y; 5,053 at 15-60y	Not reported
22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46	Hosking et al (2016) ⁵	England	HR=3.62 (3.33, 3.93) at 18-84y <i>M:</i> HR=3.30 (2.96, 3.68) at 18-84y <i>F:</i> HR=4.10 (3.61, 4.66) at 18-84y <i>With Down syndrome:</i> HR=9.21 (7.22, 11.76) <i>Without Down syndrome:</i> HR=3.19 (2.92, 3.49) <i>With epilepsy:</i> HR=6.04 (5.04, 7.24) <i>Without epilepsy:</i> HR=3.18 (2.90, 3.50) <i>With high level of support needs:</i> HR=4.77 (4.08, 5.59) <i>Without high level of support needs:</i> HR=3.28 (2.98, 3.62) <i>With autism:</i> HR=2.39 (1.45, 3.96) <i>Without autism:</i> HR=3.66 (3.37, 3.98) <i>In communal/shared homes:</i> HR=4.99 (4.36, 5.73) <i>Not in communal/shared homes:</i> HR=3.05 (2.74, 3.30)	656 at 18-84y	<i>Underlying cause at 18-84y:</i> Circulatory: 21.6%, HR=3.05 (2.56, 3.64) Respiratory: 18.8% (pneumonia and aspiration pneumonia), HR=6.68 (5.38, 8.29) Neoplasm: 14.9%, HR=1.44 (1.18, 1.76) Nervous system: 11.6%, HR=13.79 (9.70, 19.62) Digestive: 7.0%, HR=4.02 (2.92, 5.54) Congenital anomalies: 6.9%, HR could not be estimated Mental disorders: 5.3%, HR=7.99 (5.19, 12.31) External causes: 4.1%, HR=1.85 (1.26, 2.71) Genitourinary: 3.5%, HR=10.89 (6.09, 19.47) Endocrine, nutritional, and metabolic: 2.0%, HR=5.38 (2.79, 10.07) <i>Down syndrome:</i> Respiratory: 20.3% (or 42.4% if "Down syndrome" is excluded as an underlying cause of death) <i>Avoidable deaths:</i> 37% amenable (23% controls), 19% preventable (40% controls)

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Lauer (2016) ¹⁸	USA	Not reported	438 in 2012, 409 in 2013, at 18+y	<p><i>Major cause of death, 2012, 2013</i> Heart disease: 16.0%, 13.7% Neoplasm: 13.7%, 13.4% Alzheimer disease: 13.0%-12.2% (48% in Down syndrome) Aspiration pneumonia: 9.4%, 8.6% Septicaemia: 10.0%, 8.6% Chronic lower respiratory diseases: 4.6%, 6.6% Unintentional injury: 4.8%, 3.2%</p>
Troller et al (2017) ¹⁹	Australia	1.3 (1.2, 1.5) at 20+y 4.0 (3.1, 5.2) at 20-44y 2.3 (2.0, 2.7) at 45-64y 1.0 (0.8, 1.2) at 65+y M: 1.4 (1.1, 1.6) at 20+y F: 1.3 (1.1, 1.6) at 20+y	732 at 20-65+y	<p><i>Underlying cause at 20-65+y:</i> Circulatory: 18% Neoplasm: 18% Nervous: 16% Respiratory: 12% Congenital anomaly: 11% Injury and poisoning: 6% Digestive: 5% <i>Avoidable deaths: 31%</i></p>
Glover et al (2017) ⁶	England	3.18 (2.94, 3.43) at 0-99y M: 3.03 (2.73, 3.35) at 0-99y F: 3.40 (3.02, 3.81) at 0-99y 1.6 (1.2, 2.1) to 7.8 (5.4, 11.1) at 18-99y M: 1.5 (0.9, 2.2) to 6.6 (4.0, 10.1) at 18-99y F: 1.7 (1.1, 2.4) to 11.6 (6.0, 20.2) at 18-99y	664 at 0-99y	<p><i>Underlying cause at 0-99y:</i> Circulatory: 22.9% (ischaemic heart disease 37.5%, cerebrovascular 25.7%, thrombophlebitis 6.6%, cardiomyopathy 5.9%, PE 3.9%), SMR=2.8 (2.4, 3.3) Respiratory: 17.2% (pneumonia 50.0%, pneumonitis 21.0%), SMR=4.9 (4.0, 5.9) Neoplasm: 3.1% (digestive 36.8%, respiratory 13.8%, female genital tract 10.3%, lymphoid and haematopoietic 10.3%), SMR=1.1 (0.9, 1.4) Nervous: 12.8%, SMR=9.8 (7.8, 12.1) Congenital anomalies: 8.4%, SMR=72.9 (55.1, 94.7) Digestive: 7.8%, SMR=4.0 (3.0, 5.2) No ICD10 chapters had fewer than expected deaths Other common single causes: dementia 33/664, epilepsy 26/664, cerebral palsy 23/664 <i>Avoidable deaths:</i> 44.7% (41.0%, 48.5%), mostly amenable M: 50.9% (45.9%, 56.0%); F: 36.9% (31.5%, 42.5%)</p>

COPD=chronic obstructive pulmonary disease; HR=hazard ratio; ID=intellectual disabilities; OR=odds ratio; PE=pulmonary embolism; SMR=standardised mortality ratio; y=years

*Includes some individuals with IQ>70

Rates, causes, place, and predictors of mortality in adults with intellectual disabilities with and without Down syndrome: cohort study with record linkage

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Supplementary table 2. Groupings of related causes of deaths

	ICD10
Infectious diseases	
Infection	
ENTEROCOLITIS DUE TO CLOSTRIDIUM DIFFICILE	A047
SEPSIS DUE TO STAPHYLOCOCCUS AUREUS	A410
SEPSIS, UNSPECIFIED	A419
BACTERIAL INFECTION, UNSPECIFIED	A499
SUBACUTE SCLEROSING PANENCEPHALITIS	A811
CHRONIC VIRAL HEPATITIS B WITHOUT DELTA-AGENT	B181
PULMONARY CANDIDIASIS	B371
NECROTISING FASCIITIS	M726
URINARY TRACT INFECTION, SITE NOT SPECIFIED	N390
Neoplasms	
Gastrointestinal malignant neoplasms	
MALIGNANT NEOPLASM OF PAROTID GLAND	C07
MALIGNANT NEOPLASM, OESOPHAGUS, UNSPECIFIED	C159
MALIGNANT NEOPLASM, STOMACH, UNSPECIFIED	C169
MALIGNANT NEOPLASM, CAECUM	C180
MALIGNANT NEOPLASM, SIGMOID COLON	C187
MALIGNANT NEOPLASM, COLON, UNSPECIFIED	C189
INTRAHEPATIC BILE DUCT CARCINOMA	C221
NEOPLASM OF UNCERTAIN OR UNKNOWN BEHAVIOUR, OTHER DIGESTIVE ORGANS	D377
Other neoplasms	
MALIGNANT NEOPLASM, LOWER LOBE, BRONCHUS OR LUNG	C343
MALIGNANT NEOPLASM, BRONCHUS OR LUNG, UNSPECIFIED	C349
MALIGNANT NEOPLASM, BREAST, UNSPECIFIED	C509
MALIGNANT NEOPLASM, ENDOMETRIUM	C541
MALIGNANT NEOPLASM OF OVARY	C56
MALIGNANT NEOPLASM, TESTIS, UNSPECIFIED	C629
MALIGNANT NEOPLASM, BLADDER, UNSPECIFIED	C679
MALIGNANT NEOPLASMS OF THYROID GLAND	C73
WALDENSTROM MACROGLOBULINAEMIA	C880
NON-HODGKIN'S LYMPHOMA, UNSPECIFIED	C859
MALIGNANT NEOPLASM OF UNSPECIFIED SITE	C80
NEOPLASM OF UNCERTAIN OR UNKNOWN BEHAVIOUR, TRACHEA, BRONCHUS AND LUNG	D381
SECONDARY MALIGNANT NEOPLASM OF LUNG	C780
SECONDARY MALIGNANT NEOPLASM OF LIVER AND INTRAHEPATIC BILE DUCT	C787
SECONDARY MALIGNANT NEOPLASM OF BRAIN AND CEREBRAL MENINGES	C793
SECONDARY MALIGNANT NEOPLASM OF OTHER SPECIFIED SITES	C798
Endocrine and metabolic diseases	
Diabetes	
INSULIN-DEPENDENT DIABETES MELLITUS WITHOUT COMPLICATIONS	E109
NON-INSULIN-DEPENDENT DIABETES MELLITUS WITH RENAL COMPLICATIONS	E112
NON-INSULIN-DEPENDENT DIABETES MELLITUS W. PERIPHERAL CIRC. COMPLICATIONS	E115
NON-INSULIN-DEPENDENT DIABETES MELLITUS WITHOUT COMPLICATIONS	E119
UNSPECIFIED DIABETES MELLITUS WITH RENAL COMPLICATIONS	E142

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1		
2	UNSPECIFIED DIABETES MELLITUS WITHOUT COMPLICATIONS	E149
3	ABNORMAL GLUCOSE TOLERANCE TEST	R730
4	HYPERGLYCAEMIA, UNSPECIFIED	R739
5		
6	Metabolic disorders	
7	OTHER HYPERPHENYLALANINAEMIAS	E701
8	DISORDERS OF PHOSPHORUS METABOLISM & PHOSPHATASES	E833
9	DISORDERS OF PLASMA-PROTEIN METABOLISM, NOT ELSEWHERE CLASSIFIED	E880
10		
11		
12	Mental disorders	
13	Dementias	
14	VASCULAR DEMENTIA, UNSPECIFIED	F019
15	UNSPECIFIED DEMENTIA	F03
16	ALZHEIMER'S DISEASE WITH LATE ONSET	G301
17	ALZHEIMER'S DISEASE, UNSPECIFIED	G309
18		
19	Mental health	
20		
21	MENTAL AND BEHAVIOURAL DISORDERS DUE TO ACUTE INTOXICATION WITH ALCOHOL	F100
22	MENTAL AND BEHAVIOURAL DISORDERS DUE TO ALCOHOL DEPENDENCE SYNDROME	F102
23	MENTAL AND BEHAVIOURAL DISORDERS DUE TO USE OF TOBACCO, UNSPECIFIED	F179
24	SCHIZOPHRENIA, UNSPECIFIED	F209
25	BIPOLAR AFFECTIVE DISORDER, UNSPECIFIED	F319
26	OTHER & UNSPEC SYMPTOMS & SIGNS INVOLVING COGNITIVE FUNCTIONS &	R418
27	AWARENESS	
28	INTENTIONAL SELF-HARM BY JUMPING FROM A HIGH PLACE	X80
29		
30	Intellectual disabilities	
31	UNSPECIFIED MENTAL RETARDATION	F79
32	DEVELOPMENTAL DISORDER OF SCHOLASTIC SKILLS, UNSPECIFIED	F819
33		
34		
35	Nervous system	
36	Epilepsies	
37	GENERALIZED IDIOPATHIC EPILEPSY AND EPILEPTIC SYNDROMES	G403
38	EPILEPSY, UNSPECIFIED	G409
39	STATUS EPILEPTICUS, UNSPECIFIED	G419
40	MYOTONIC DISORDERS	G711
41	OTHER AND UNSPECIFIED CONVULSIONS	R568
42		
43	Cerebral palsy	
44	SPASTIC QUADRAPLEGIC CEREBRAL PALSY	G800
45	SPASTIC HEMIPLEGIC CEREBRAL PALSY	G802
46	OTHER CEREBRAL PALSY	G808
47	CEREBRAL PALSY, UNSPECIFIED	G809
48	TETRAPLEGIA, UNSPECIFIED	G825
49		
50	Other neurological conditions	
51	SEQUELAE OF INFLAMMATORY DISEASES OF CENTRAL NERVOUS SYSTEM	G09
52	PARKINSON'S DISEASE	G20
53	MYONEURAL DISORDER, UNSPECIFIED	G709
54	ENCEPHALITIS, MYELITIS AND ENCEPHALOMYELITIS, UNSPECIFIED	G049
55	ANOXIC BRAIN DAMAGE, NOT ELSEWHERE CLASSIFIED	G931
56	BLINDNESS, BINOCULAR	H540
57	OTHER DISORDERS OF NERVOUS SYSTEM, NOT ELSEWHERE CLASSIFIED	G98
58		
59		
60		

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Circulatory system

Acute myocardial infarction

ACUTE MYOCARDIAL INFARCTION, UNSPECIFIED I219

CARDIAC ARRECT, UNSPECIFIED I469

Other ischaemic heart disease

HYPERTENSIVE HEART DISEASE WITHOUT (CONGESTIVE) HEART FAILURE I119

ACUTE ISCHAEMIC HEART DISEASE, UNSPECIFIED I249

ATHEROSCLEROTIC HEART DISEASE I251

CHRONIC ISCHAEMIC HEART DISEASE, UNSPECIFIED I259

ATHEROSCLEROSIS OF AORTA I700

GENERALIZED AND UNSPECIFIED ATHEROSCLEROSIS I709

Heart failure

HEART FAILURE, UNSPECIFIED I509

LEFT VENTRICULAR FAILURE I501

CONGESTIVE HEART FAILURE I500

Other cardiovascular disease

PULMONARY EMBOLISM WITHOUT MENTION OF ACUTE COR PULMONALE I269

OTHER SPECIFIED PULMONARY HEART DISEASES I278

PULMONARY HEART DISEASE, UNSPECIFIED I279

AORTIC (VALVE) STENOSIS I350

ATRIAL FIBRILLATION AND FLUTTER I48

VENTRICULAR FIBRILLATION AND FLUTTER I490

OTHER ILL-DEFINED HEART DISEASES I518

PULMONARY OEDEMA J81

CARDIOGENIC SHOCK R570

PERIPHERAL VASCULAR DISEASE, UNSPECIFIED I739

PHLEBITIS AND THROMBOPHLEBITIS OF OTHER DEEP VESSELS OF LOWER EXTREMITIES I802

EMBOLISM AND THROMBOSIS OF OTHER SPECIFIED VEINS I828

ACUTE AND SUBACUTE INFECTIVE ENDOCARDITIS I330

ACUTE ENDOCARDITIS, UNSPECIFIED I339

ENDOCARDITIS, VALVE UNSPECIFIED I38

DILATED CARDIOMYOPATHY I420

CARDIOMEGALY I517

ESSENTIAL (PRIMARY) HYPERTENSION I10

Stroke

INTRACEREBRAL HAEMORRHAGE, UNSPECIFIED I619

CEREBRAL INFARCTION DUE TO THROMBOSIS OF PRECEREBRAL ARTERIES I630

CEREB INFARCT DUE TO UNSPEC OCCL/STENOSIS OF PRECEREB ARTERIES I632

CEREBRAL INFARCTION, UNSPECIFIED I639

STROKE, NOT SPECIFIED AS HAEMORRHAGE OR INFARCTION I64

CEREBROVASCULAR DISEASE, UNSPECIFIED I679

SEQUELAE OF STROKE, NOT SPECIFIED AS HAEMORRHAGE OR INFARCTION I694

SEQUELAE OF OTHER AND UNSPECIFIED CEREBROVASCULAR DISEASES I698

Respiratory system

Respiratory infection

ACUTE UPPER RESPIRATORY INFECTION, UNSPECIFIED J069

INFLUENZA WITH PNEUMONIA, OTHER INFLUENZA VIRUS IDENTIFIED J100

INFLUENZA WITH OTHER RESP MANIFESTATIONS, OTHER INFLUENZA VIRUS IDENTIFIED J101

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1		
2	PNEUMONIA DUE TO STREPTOCOCCUS PNEUMONIAE	J13
3	BRONCHOPNEUMONIA, UNSPECIFIED	J180
4	LOBAR PNEUMONIA, UNSPECIFIED	J181
5	HYPOSTATIC PNEUMONIA, UNSPECIFIED	J182
6	PNEUMONIA, UNSPECIFIED	J189
7	UNSPECIFIED ACUTE LOWER RESPIRATORY INFECTION	J22
8	CHRONIC OBSTRUCTIVE PULMONARY DISEASE WITH ACUTE LOWER RESP INFECTION	J440
9		
10		
11	Aspiration/reflux/choking	
12	PNEUMONITIS DUE TO FOOD AND VOMIT	J690
13	GASTRO-OESOPHAGEAL REFLUX DISEASE WITHOUT OESOPHAGITIS	K219
14	INHALATION AND INGESTION OF FOOD CAUSING OBSTRUCTION OF RESPIRATORY	W79
15	TRACT	
16		
17	FOREIGN BODY IN RESPIRATORY TRACT, PART UNSPECIFIED	T179
18	INHALATION/INGESTION OF OTHER OBJECTS CAUSING OBSTRUCT OF RESP TRACT	W80
19		
20	Other respiratory disorders	
21	UNSPECIFIED CHRONIC BRONCHITIS	J42
22	EMPHYSEMA, UNSPECIFIED	J439
23	CHRONIC OBSTRUCTIVE PULMONARY DISEASE, UNSPECIFIED	J440
24	ASTHMA, UNSPECIFIED	J459
25	BRONCHIECTASIS	J47
26	OTHER INTERSTITIAL PULMONARY DISEASES WITH FIBROSIS	J841
27	PLEURAL EFFUSION, NOT ELSEWHERE CLASSIFIED	J90
28	CHRONIC RESPIRATORY FAILURE	J961
29	RESPIRATORY FAILURE, UNSPECIFIED	J969
30	OTHER SPECIFIED RESPIRATORY DISORDERS	J988
31	DYSPNOEA	R060
32	RESPIRATORY ARREST	R092
33	ASPHYXIATION	T71
34	UNSPECIFIED THREAT TO BREATHING	W84
35		
36		
37		
38		
39	Digestive system	
40	Ulcer/gastrointestinal perforation	
41	OESOPHAGITIS	K20
42	PERFORATION OF INTESTINE (NONTRAUMATIC)	K631
43	PERITONITIS, UNSPECIFIED	K659
44	GASTRIC ULCER, CHRONIC OR UNSPECIFIED WITH PERFORATION	K255
45	OTHER PERITONITIS	K658
46	ACUTE PERITONITIS	K650
47	GASTROINTESTINAL HAEMORRHAGE, UNSPECIFIED	K922
48	ULCER OF INTESTINE	K633
49		
50	Other gastrointestinal disorders	
51	BARRETTS OESOPHAGUS	K227
52	DIAPHRAGMATIC HERNIA WITHOUT OBSTRUCTION OR GANGRENE	K449
53	OTHER SPECIFIED NONINFECTIVE GASTROENTERITIS AND COLITIS	K528
54	ACUTE VASCULAR DISORDERS OF INTESTINE	K550
55	VASCULAR DISORDER OF INTESTINE, UNSPECIFIED	K559
56	VOLVULUS	K562
57	OTHER AND UNSPECIFIED INTESTINAL OBSTRUCTION	K566
58	CONSTIPATION	K590
59		
60		

Rates, causes, place, and predictors of mortality in adults with intellectual disabilities with and without Down syndrome: cohort study with record linkage

MEGACOLON, NOT ELSEWHERE CLASSIFIED	K593
ACUTE AND SUBACUTE HEPATIC FAILURE	K720
OTHER AND UNSPECIFIED CIRRHOSIS OF LIVER	K746
AUTOIMMUNE HEPATITIS	K754
INFLAMMATORY LIVER DISEASE, UNSPECIFIED	K759
OTHER SPECIFIED DISEASES OF LIVER	K768
CALCULUS OF GALLBLADDER WITH OTHER CHOLECYSTITIS	K801
CHOLANGITIS	K830
ACUTE PANCREATITIS, UNSPECIFIED	K859
PSEUDOCYST OF PANCREAS	K863
INTESTINAL MALABSORPTION, UNSPECIFIED	K909
DYSPHAGIA	R13

Genitourinary system

Renal failure

CHRONIC NEPHRITIC SYNDROME, UNSPECIFIED	N039
OTHER ACUTE RENAL FAILURE	N178
ACUTE RENAL FAILURE, UNSPECIFIED	N179
END-STAGE RENAL DISEASE	N180
CHRONIC KIDNEY DISEASE, STAGE 5	N185
CHRONIC KIDNEY DISEASE, UNSPECIFIED	N189
UNSPECIFIED KIDNEY FAILURE	N19

Chromosomal abnormalities

Down syndrome

DOWN'S SYNDROME, UNSPECIFIED	Q909
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Other congenital condition

CONGENITAL HYDROCEPHALUS, UNSPECIFIED	Q039
SPINA BIFIDA, UNSPECIFIED	Q059
CONGENITAL MALFORMATION OF HEART, UNSPECIFIED	Q249
CONGENITAL DEFORMITY OF SPINE	Q675
CONGEN MALFORMATION SYNDROMES PREDOMINANTLY ASSOCIATED WITH SHORT STATURE	Q871
MARFAN'S SYNDROME	Q874
OTHER SPECIFIED CONGEN MALFORMATION SYNDROMES, NOT ELSEWHERE CLASSIFIED	Q878
CONGENITAL MALFORMATION, UNSPECIFIED	Q899
KLINEFELTER'S SYNDROME, UNSPECIFIED	Q984
FRAGILE X CHROMOSOME	Q992
OTHER LACK OF EXPECTED NORMAL PHYSIOLOGICAL DEVELOPMENT	R628

Other conditions occurring with small frequency

Other condition

DECUBITUS ULCER AND PRESSURE AREA	L89
SCOLIOSIS, UNSPECIFIED	M419
URETHRAL STRICTURE, UNSPECIFIED	N359
EPISTAXIS	R040
IMMOBILITY	R263
MALAISE AND FATIGUE	R53
GENERALIZED ENLARGED LYMPH NODES	R591

Rates, causes, place, and predictors of mortality in adults with intellectual disabilities with and without Down syndrome: cohort study with record linkage

1		
2	INSUFFICIENT INTAKE OF FOOD AND WATER DUE TO SELF NEGLECT	R636
3	OTHER SPECIFIED GENERAL SYMPTOMS AND SIGNS	R688
4	OTHER ILL-DEFINED AND UNSPECIFIED CAUSES OF MORTALITY	R99
5	EXPOSURE TO UNSPECIFIED FACTOR	X59
6	MULTI-SYSTEM DEGENERATION	G903
7	BENIGN NEOPLASM, MENINGES, UNSPECIFIED	D329
8	AGRANULOCYTOSIS	D70
9	SARCOIDOSIS OF OTHER AND COMBINED SITES	D868
10	SARCOIDOSIS, UNSPECIFIED	D869
11	HYPOPITUITARISM	E230
12	HYPOTHYROIDISM, UNSPECIFIED	E039
13	OTHER THYROTOXICOSIS	E058
14	VOLUME DEPLETION	E86
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20	Injuries and external causes	
21	Injuries and accidents	
22	INTRACRANIAL INJURY, UNSPECIFIED	S069
23	UNSPECIFIED INJURY OF HEAD	S099
24	INJURY OF COLON	S365
25	FRACTURE OF NECK OF FEMUR	S720
26	FRACTURE OF SHAFT OF TIBIA	S822
27	UNSPECIFIED MULTIPLE INJURIES	T07
28	FAT EMBOLISM (TRAUMATIC)	T791
29	SEQUELAE OF UNSPECIFIED INJURY OF HEAD	T909
30	UNSPECIFIED FALL	W19
31	SEQUELAE OF OTHER ACCIDENTS	Y86
32		
33		
34		
35	Medical/surgical complication	
36	POISONING BY OTHER ANTIDYSRHYTHMIC DRUGS, NOT ELSEWHERE CLASSIFIED	T462
37	ADVERSE EFFECTS OF OTHER ANTIDYSRHYTHMIC DRUGS, NOT ELSEWHERE CLASSIFIED	Y522
38	ABN REACT TO/LATER COMPLIC OF OP WITH IMPLANT OF ARTIFICIAL INTERN DEVICE	Y831
39	ABN REACT TO/LATER COMPLIC OF OP WITH ANASTOMOSIS, BYPASS OR GRAFT	Y832
40	ABN REACT TO/LATER COMPLIC OF OP WITH FORMATION OF EXTERNAL STOMA	Y833
41	ABNORMAL REACTION TO OR LATER COMPLICATION OF OTHER MEDICAL PROCEDURES	Y848
42	SEQ OF PROCED CAUSING ABN REACT/COMPLIC,W/O MENTION OF MISADV AT THE TIME	Y883
43	OTHER POSTPROCEDURAL RESPIRATORY DISORDERS	J958
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Rates, causes, place, and predictors of mortality in adults with intellectual disabilities with and without Down syndrome: cohort study with record linkage

Supplementary table 3. Predictors of the outcome time to death from univariate analyses

Variable		N with event/ N in group	Hazard ratio (95% CI)	Individual p-value	Overall p-value
Demographics					
Age at time of health assessment		294/961	1.05 (1.04, 1.06)	<0.0001	
Sex	Male	154/525	0.88 (0.70, 1.11)	0.2730	
	Female	140/436	1.00 (-)		
Ability level	Mild ID	92/382	1.00 (-)		0.0007
	Moderate ID	73/236	1.38 (1.01, 1.87)	0.0411	
	Severe ID	67/180	1.75 (1.28, 2.40)	0.0005	
	Profound ID	62/163	1.77 (1.28, 2.45)	0.0005	
Type of accommodation	Family carer	70/374	1.00 (-)		<0.0001
	Independent of care	36/93	2.35 (1.57, 3.52)	<0.0001	
	Paid support	161/435	2.18 (1.65, 2.88)	<0.0001	
	Congregate	27/59	2.87 (1.84, 4.48)	<0.0001	
Neighbourhood deprivation	1 - most affluent	18/73	1.00 (-)		0.1890
	2	56/137	1.92 (1.13, 3.27)	0.0158	
	3	10/45	0.90 (0.42, 1.95)	0.7896	
	4	10/40	1.06 (0.49, 2.30)	0.8808	
	5	12/32	1.71 (0.82, 3.55)	0.1527	
	6	9/32	1.27 (0.57, 2.82)	0.5640	
	7	9/34	1.09 (0.49, 2.43)	0.8302	
	8	15/58	1.21 (0.61, 2.41)	0.5818	
	9	35/124	1.22 (0.69, 2.16)	0.4882	
	10 - most deprived	120/386	1.41 (0.86, 2.31)	0.1782	
Civil status	Single	288/938	1.28 (0.57, 2.87)	0.5485	
	Not single	6/23	1.00 (-)		
Employment/day activities	Yes	83/231	1.33 (1.03, 1.71)	0.0284	
	No	211/730	1.00 (-)		
Smoker	Yes	46/101	1.70 (1.24, 2.33)	0.0009	
	No	248/860	1.00 (-)		
Health					
Down syndrome	Yes	64/179	1.30 (0.98, 1.71)	0.0673	
	No	230/782	1.00 (-)		
Epilepsy	Yes	111/325	1.25 (0.99, 1.58)	0.0636	
	No	183/636	1.00 (-)		
Spastic quadriplegia	Yes	24/325	1.67 (1.10, 2.54)	0.0158	
	No	183/636	1.00 (-)		
Impaired mobility	Yes	195/735	0.51 (0.40, 0.65)	<0.0001	
	No	99/226	1.00 (-)		
Body mass index	Underweight	9/43	0.63 (0.32, 1.25)	0.1847	0.1865
	Acceptable	83/265	1.00 (-)		
	Overweight	75/289	0.78 (0.57, 1.06)	0.1132	
	Obese	81/237	1.08 (0.80, 1.47)	0.6152	
	Morbidly obese	16/58	0.87 (0.51, 1.48)	0.6058	
Hearing impairment	Yes	112/267	1.79 (1.41, 2.26)	<0.0001	
	No	182/694	1.00 (-)		
Visual impairment	Yes	154/449	1.29 (1.02, 1.62)	0.0317	
	No	140/512	1.00 (-)		

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Urinary incontinence	Yes	158/632	0.52 (0.41, 0.65)	<0.0001	
	No	136/329	1.00 (-)		
Bowel incontinence	Yes	197/733	0.55 (0.43, 0.70)	<0.0001	
	No	97/228	1.00 (-)		
Diabetes	Yes	29/47	2.72 (1.86, 4.00)	<0.0001	
	No	265/914	1.00 (-)		
PEG/tube fed	Yes	N/7	4.99 (2.22, 11.20)	0.0001	
	No	288/954			
Constipation	Yes	112/316	1.34 (1.06, 1.70)	0.0145	
	No	182/645	1.00 (-)		
Ataxia/gait disorder	Yes	104/276	1.50 (1.18, 1.90)	0.0009	
	No	190/685	1.00 (-)		
Nail disorder	Yes	74/223	1.18 (0.91, 1.54)	0.2120	
	No	220/738	1.00 (-)		
Epidermal thickening	Yes	66/207	1.10 (0.84, 1.45)	0.4947	
	No	228/754	1.00 (-)		
Cerebral palsy	Yes	54/175	1.02 (0.76, 1.37)	0.8792	
	No	240/786	1.00 (-)		
Osteoporosis	Yes	76/174	1.71 (1.32, 2.22)	<0.0001	
	No	218/786	1.00 (-)		
Fungal infection	Yes	42/158	0.83 (0.61, 1.18)	0.3366	
	No	252/803	1.00 (-)		
Hypertension	Yes	56/146	1.36 (1.01, 1.82)	0.0399	
	No	238/815	1.00 (-)		
Dysphagia	Yes	51/132	1.51 (1.11, 2.04)	0.0080	
	No	243/829	1.00 (-)		
Dyspnoea	Yes	49/130	1.41 (1.04, 1.92)	0.0285	
	No	245/831	1.00 (-)		
Musculoskeletal pain	Yes	48/148	1.14 (0.83, 1.55)	0.4153	
	No	246/813	1.00 (-)		
Bone deformity	Yes	50/139	1.32 (0.97, 1.79)	0.0769	
	No	244/822	1.00 (-)		
Dental/oral problem	Yes	38/120	1.07 (0.76, 1.50)	0.7128	
	No	256/841	1.00 (-)		
Eczema/dermatitis	Yes	38/138	0.86 (0.61, 1.21)	0.3790	
	No	256/823	1.00 (-)		
GORD	Yes	51/133	1.43 (1.06, 1.94)	0.0198	
	No	243/828	1.00 (-)		
Lower respiratory tract infection	Yes	55/126	1.75 (1.30, 2.34)	0.0002	
	No	239/835	1.00 (-)		
Total number of physical conditions		294/961	1.06 (1.04, 1.08)	<0.0001	
Psychosis	Yes	11 /42	0.81 (0.44, 1.48)	0.4990	
	No	283 /919	1.00 (-)		
Affective disorder including bipolar	Yes	24/68	1.19 (0.78, 1.80)	0.4216	
	No	270/893	1.00 (-)		
Autism	Yes	13/69	0.54 (0.31, 0.94)	0.0306	
	No	281/892	1.00 (-)		
Problem behaviour	Yes	71/218	1.09 (0.83, 1.42)	0.5251	
	No	223/743	1.00 (-)		
Eating disorder, including pica	Yes	5/17	0.99 (0.41, 2.40)	0.9857	
	No	289/944	1.00 (-)		
Any mental illness, excluding problem behaviours	Yes	73/217	1.16 (0.89, 1.51)	0.2849	
	No	221/744	1.00 (-)		
Service use					
Number of GP consultations in last 12 months		287/951	1.05 (1.03, 1.06)	<0.0001	

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Number of A&E attendances in last 12 months		280/938	1.09 (0.99, 1.20)	0.0847	
Number of health professions providing care		294/961	1.10 (1.03, 1.16)	0.0023	
Prescriptions					
Antipsychotics	Yes	79/226	1.12 (0.94, 1.57)	0.1421	
	No	215/735	1.00 (-)		
Antidepressants	Yes	39/118	1.16 (0.83, 1.63)	0.3778	
	No	255/843	1.00 (-)		
Anxiolytic/hypnotics	Yes	20/68	0.95 (0.60, 1.49)	0.8159	
	No	274/893	1.00 (-)		
Antiepileptics	Yes	90/253	1.31 (1.02, 1.68)	0.0315	
	No	204/708	1.00 (-)		
Number of drug classes taken		294/961	1.16 (1.12, 1.21)	<0.0001	

A&E=accident and emergency; CI=confidence interval; GORD=gastro-oesophageal reflux disorder; PEG=percutaneous endoscopic gastrostomy

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No.	Recommendation	Page No.	Relevant text from manuscript
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract		p1
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found		p2
Introduction				
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported		p4-6, supplementary table 1
Objectives	3	State specific objectives, including any prespecified hypotheses		6, paragraph 3
Methods				
Study design	4	Present key elements of study design early in the paper		p6-10, supplementary tables 2/3
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection		p7, paragraph 1, 7-8
Participants	6	(a) <i>Cohort study</i> —Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up <i>Case-control study</i> —Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls <i>Cross-sectional study</i> —Give the eligibility criteria, and the sources and methods of selection of participants		p7, paragraph 1
		(b) <i>Cohort study</i> —For matched studies, give matching criteria and number of exposed and unexposed <i>Case-control study</i> —For matched studies, give matching criteria and the number of controls per case		p7, paragraph 2, p9, paragraph 4
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable		p7-8, supplementary table 2
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group		p7-8, p9, paragraph 4
Bias	9	Describe any efforts to address potential sources of bias		p9, paragraph 4
Study size	10	Explain how the study size was arrived at		P7, paragraph2, p9, paragraph 4

Continued on next page

Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	p8-10
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	p8-10
		(b) Describe any methods used to examine subgroups and interactions	p8-10
		(c) Explain how missing data were addressed	p11, paragraph 2
		(d) <i>Cohort study</i> —If applicable, explain how loss to follow-up was addressed	p11, paragraph 2
		<i>Case-control study</i> —If applicable, explain how matching of cases and controls was addressed	
		<i>Cross-sectional study</i> —If applicable, describe analytical methods taking account of sampling strategy	
		(e) Describe any sensitivity analyses	N/A
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	p11, paragraph 2
		(b) Give reasons for non-participation at each stage	p11, paragraph 2
		(c) Consider use of a flow diagram	-
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	p11-12, Table 1, supplementary table 3
		(b) Indicate number of participants with missing data for each variable of interest	table 1, supplementary table 3
		(c) <i>Cohort study</i> —Summarise follow-up time (eg, average and total amount)	p12, paragraph 1
Outcome data	15*	<i>Cohort study</i> —Report numbers of outcome events or summary measures over time	p11, paragraph 2
		<i>Case-control study</i> —Report numbers in each exposure category, or summary measures of exposure	
		<i>Cross-sectional study</i> —Report numbers of outcome events or summary measures	
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	P15, table 6
		(b) Report category boundaries when continuous variables were categorized	N/A
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	-

Continued on next page

Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	p11-16
Discussion			
Key results	18	Summarise key results with reference to study objectives	p16, paragraph 2
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	p20, paragraph 1
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	p20, paragraph 2
Generalisability	21	Discuss the generalisability (external validity) of the study results	p20, paragraph 1
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	P24

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at www.strobe-statement.org.