

# Mortality due to cardiovascular disease, respiratory disease, and cancer in adults with cerebral palsy

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## ABBREVIATIONS

CPRD	Clinical Practice Research Datalink
ONS	Office for National Statistics
SMR	Standardized mortality ratio

**AIM** To compare mortality rates for cardiovascular disease, cancer, and respiratory disease between adults with cerebral palsy (CP) and the general population.

**METHOD** A cohort study was conducted using data from adults with CP in England, identified through a primary care data set (the Clinical Practice Research Datalink), with linked data on death registrations from the Office for National Statistics. Cause of death was categorized according to International Classification of Diseases codes. Standardized mortality ratios (SMRs) were calculated to compare mortality rates between adults with CP and the general population, adjusted for age, sex, and calendar year.

**RESULTS** Nine hundred and fifty-eight adults with CP were identified (52.5% males, 47.5% females; median age at start of follow-up 31y [interquartile range 22–43y]) and followed for a total of 7693 person-years. One hundred and forty-two patients (15%) died during follow-up. Adults with CP had an increased risk of death due to cardiovascular disease (SMR: 3.19, 95% confidence interval [CI] 2.20–4.62) and respiratory disease (SMR: 13.59, 95% CI 9.89–18.67), but not from malignant neoplasms (SMR: 1.42, 95% CI 0.83–2.45).

**INTERPRETATION** We found that adults with CP in England have increased risk of death due to diseases of the circulatory and respiratory systems, supporting findings from two studies that compared cause-specific mortality rates between adults with CP in the USA and the general population. Further research is required into primary and secondary prevention of cardiovascular and respiratory disease in people with CP worldwide.

There have been substantial improvements in survival rates observed among children with cerebral palsy (CP) in recent decades.<sup>1</sup> Mortality rates among children aged less than 15 years in the USA have improved at a rate of approximately 1.5 per cent per year since the 1980s, which is in line with improvements in the general population.<sup>1</sup> Therefore, although CP was historically considered a paediatric condition, the majority of children are now expected to live to adulthood.<sup>2,3</sup> Mortality rates among adolescents and adults with CP who feed orally, however, have not declined in recent decades.<sup>1</sup> As a result, there is a widening gap in life expectancy between adults with CP and the general population;<sup>1</sup> the ratio of mortality rates for these adults with CP to mortality rates in the general population has increased by 1.7 per cent yearly since the 1980s.<sup>1</sup>

Causes of death among adults with CP have not been widely examined. In 1999, Strauss et al.<sup>4</sup> reported that adults with CP in the USA had an increased risk of death

due to ischaemic heart disease, cerebrovascular disease, cancer, pneumonia, chronic obstructive pulmonary disease, and diseases of the digestive system. Although respiratory disease is often considered the leading cause of mortality among children with CP,<sup>3,5</sup> Strauss et al.<sup>4</sup> reported that, similar to the general population, diseases of the circulatory system were the leading cause of death among adults with CP. A later study of adults in the USA also found that adults with CP had a higher risk of mortality due to cancer.<sup>6</sup> Other studies describing cause of death in adults with CP outside of the USA suggested that diseases of the respiratory system were the leading cause of death.<sup>7,8</sup> These studies however did not directly compare cause-specific mortality rates between people with and without CP and so limited conclusions can be drawn regarding relative risk.

Cardiovascular disease, chronic respiratory disease, and cancer are leading causes of death worldwide.<sup>9</sup> The

potential causal pathway between CP and these diseases has not been explored. However, physical inactivity is a shared risk factor for these diseases. It is well established that people with CP participate in reduced physical activity throughout their lifespan,<sup>10</sup> which may partly explain excess mortality. Additional explanations for an increased risk of mortality in adults with CP may be poor diagnosis and management of these conditions. While management of cardiovascular disease, chronic respiratory disease, and cancer in people with CP has not been explored,<sup>10</sup> it may be hypothesized that various factors including communication difficulties, difficulties accessing health services, or diagnostic overshadowing result in poorer management among people with CP.

While it is plausible that adults with CP have increased risk of mortality due to cardiovascular disease, respiratory disease, and cancer, only one study has compared the incidence of mortality due to these conditions in adults with CP to the incidence in the general population.<sup>4</sup> Since that study, associations between CP and mortality due to these conditions have not been examined in populations outside of the USA. The aim of this study was therefore to compare mortality rates for cardiovascular disease, cancer, and respiratory disease between adults with CP and the general population.

## METHOD

A cohort study was conducted to compare mortality rates due to cardiovascular disease, respiratory disease, and cancer in adults with CP to the general population. The Clinical Practice Research Datalink (CPRD), a primary care data set, was used to identify patients with CP in England with linked data on death registrations from the Office for National Statistics (ONS).

Data in the CPRD are collected via electronic health records from 674 general practices across all regions of the UK every month.<sup>11</sup> As of 2013, the CPRD included research standard data on 11.3 million patients (approximately 18% of the UK population).<sup>11</sup> Linked data from the ONS are available for patients from a subset of practices in England (75% of participating practices in England as of 2013, representing 58% of all UK participating practices).<sup>11</sup> General practitioners are the gatekeepers of health care in the UK. Nearly 99 per cent of people in England are registered with a general practitioner<sup>12</sup> and visits to a general practitioner are free of charge. Although general practitioners may refer patients to secondary care, patient data are fed back from secondary care to general practitioners and recorded against a unique National Health Service patient identifier. Data from the CPRD are largely representative of the UK population in terms of age, sex, and ethnicity, but general practices contributing to the CPRD may not be representative of all practices in the UK in terms of size.<sup>11,13,14</sup> Routine data collected on all patients, such as clinical diagnoses, referrals, and therapies, are provided to the CPRD, unless a patient opts out. Clinical events are recorded in general practice systems in the

## What this paper adds

- Adults with cerebral palsy (CP) in England have 14-fold increased risk of mortality due to diseases of the respiratory system.
- They have a 3-fold increased risk of mortality due to diseases of the circulatory system.
- Adults with CP had an increased risk of death due to cerebrovascular disease and ischaemic heart disease.
- The elevated risk of ischaemic heart disease, however, did not reach statistical significance at the 5% per cent level.

UK using a Read code. The Read clinical classification is a hierarchical system of recording clinical data. Read codes consist of five letters and numbers and are accompanied by a Read term that provides a written description of the condition each Read code refers to.

Data from the CPRD are linked to ONS death registration data by an independent third party using an eight-step algorithm, based on exact National Health Service number, sex, date of birth, and postcode. It is a legal requirement that all deaths in England are registered; deaths are usually registered within 5 days of the date of death. Cause of death is provided by a medical practitioner.<sup>15</sup> Causes of death are coded according to the International Classification of Diseases (ICD). The 10th revision of the ICD (ICD-10) has been used to code cause of death in England since 2001. Before 2001 ICD-9 codes were used. Information on death registrations was available for patients for the period 2nd January 1998 to 31st December 2015.

## Participants

Adults in England with a diagnosis of CP were identified using Read codes for CP (Appendix S1, online supporting information). The start of follow-up for patients with CP was set to the latest of: (1) 2nd January 1998; (2) the date the patient registered with the general practice; (3) the practice up-to-standard date (i.e. the date that data were considered of sufficient quality to be used for research purposes); and (4) the first January of the year in which the patient turned 18 years. Patients were followed to the earliest of: (1) transfer out of the CPRD; (2) 31st December 2015; (3) the practice last collection date; and (4) the date of death provided by the ONS.

The underlying cause of death was categorized according to the revision of ICD codes in use at date of death (i.e. ICD-9 or ICD-10). Where the underlying cause of death was coded as CP (ICD-10 code G80) and more than one cause of death was recorded, the cause of death preceding the underlying cause of death (i.e. CP) was used for analyses. The underlying cause of death was broadly categorized as death due to malignant neoplasms (C00–C97), diseases of the circulatory system (I00–I99), and diseases of the respiratory system (J00–J99). Within these categories cause of death was categorized as colorectal cancer (C18–C21), lung cancer (C33–C34), breast cancer (C50), prostate cancer (C61), hypertensive diseases (I10–I15), ischaemic heart diseases (I20–I25), cerebrovascular diseases (I60–I69), heart failure (I50), chronic obstructive pulmonary disease (J40–J44), and asthma (J45). Because of data restrictions

designed to preserve anonymity, we reported specific causes of death only if more than five deaths were observed for a given cause in patients with CP.

For each cause of death, we identified age-, sex-, and calendar year-specific mortality rates in the general population from data on death registrations published annually by the ONS.<sup>16</sup> This allowed us to compare age-, sex-, and calendar year-specific mortality rates between adults with CP and the general population.

### Statistical analysis

Means, standard deviations, medians, interquartile ranges, ranges, frequencies, and percentages, where appropriate, were used to describe the distribution of sex, age at start of follow-up, and general practice location among patients with CP. The number and percentage of patients with CP who died during follow-up, the number and percentage of patients with CP who died of each cause, and the total number of person-years of follow-up were calculated.

All cause and cause-specific standardized mortality ratios (SMRs) were calculated as the number of observed deaths divided by the number of expected deaths within each category of causes. In order to obtain the number of expected deaths, person-years of follow-up was stratified according to sex, age (10y bands), and calendar year (1y bands) and multiplied by the corresponding sex-, age-, and calendar year-specific mortality rate for the general population.<sup>16</sup> Expected numbers of deaths in each stratum were then summed to obtain the overall sex-, age-, and calendar year-adjusted expected number. Stata version 14 (Statcorp, College Station, TX, USA) was used to conduct analysis.

### RESULTS

In total, we identified 958 patients with at least one record of CP who were eligible to be linked to ONS data (Table I). There were slightly more males (503, 52.5%) than females (455, 47.5%). Median (interquartile range) age at the start of follow-up was 31 years (22–43y). The cohort was followed for 7693 person-years, with median follow-up of 7 years 2 months per person (range 1mo–18y). Overall, 142 patients (15%) died while under observation. The median age of death was 40 years (range 18–97y). Slightly more males than females died during follow-up (50.7%). CP was listed as the underlying cause of death for 37 patients. In these cases, cause of death was reclassified as the cause of death preceding the underlying cause of death (i.e. CP) when one existed. Overall, 26.8 per cent of deaths ( $n=38$ ) were due to diseases of the respiratory system, 19.7 per cent of deaths ( $n=28$ ) were due to diseases of the circulatory system, and 9.2 per cent of deaths ( $n=13$ ) were due to malignant neoplasms. Patients with CP experienced 4.3 (95% CI 3.7–5.1) times the number of deaths expected in the general population during the same follow-up period (Table II). There was evidence at the 5 per cent level that they had increased risk of death due to diseases of the circulatory system (SMR: 3.19, 95% CI 2.20–4.62) and diseases of the respiratory system (SMR:

**Table I:** Patient characteristics at start of follow-up and person-years of follow-up by characteristic

Characteristic	Total ( $n=958$ )	Total person-years of follow-up
<b>Sex</b>		
Males	503 (52.5)	4182
Females	455 (47.5)	3511
<b>Age, y</b>		
Median (IQR)	31 (22–43)	–
<30	452 (47.2)	3463
30–39	206 (21.5)	1875
40–49	133 (13.9)	1191
50–59	98 (10.2)	787
≥60	69 (7.2)	376
<b>Practice region<sup>a</sup></b>		
North England	265 (27.7)	2384
Midlands	256 (26.7)	2052
South England	437 (45.6)	3258

<sup>a</sup>North England: North East England, North West England, Yorkshire. Midlands: East Midlands, West Midlands, East of England. South England: South West England, South Central England, London, South East England. IQR, interquartile range.

13.59, 95% CI 9.89–18.67) but not due to malignant neoplasms (SMR: 1.42, 95% CI 0.83–2.45). Specifically, patients with CP had an increased risk of death due to cerebrovascular diseases (SMR: 3.45, 95% CI 1.73–6.90) and ischaemic heart disease (SMR: 1.79, 95% CI 0.93–3.45; Table II).

### DISCUSSION

The results of this study demonstrate that adults with CP in England have approximately a 14-fold increased risk of death due to diseases of the respiratory system and a 3-fold increased risk of death due to diseases of the circulatory system. There was no evidence that they had increased risk of death due to cancer. When considering specific diseases of the circulatory system, there was evidence that they had increased risk of cerebrovascular disease. Although the risk of ischaemic heart disease in adults with CP was 1.8 times that in the general population, there was no statistical evidence at the 5 per cent level to support this.

Only one study has examined the cause of death in adults with CP in the UK to date.<sup>7</sup> In 2006, Hemming et al. reported the proportion of deaths due to neoplasms, diseases of the respiratory system, and diseases of the circulatory system respectively, in people with CP in 10-year age bands (20–59y). The authors provided comparative figures for the general UK population. The proportion of deaths due to neoplasms was similar or lower in people with CP at all age-groups compared to the general population (0%–24% in people with CP). The proportion of deaths due to diseases of the circulatory system was similar or slightly lower in people with CP at 20 years to 29 years, 40 years to 49 years, and 50 years to 59 years, but higher at 30 years to 39 years (17% vs 9%). The proportion of deaths due to diseases of the respiratory system was higher among people with CP at 20 years to 29 years and 30 years to 39 years (50% vs 3% and 42% vs 3% respectively), but similar at 40 years to 49 years and 50 years to

**Table II:** Observed and expected deaths and standardized mortality ratios

Cause of death	Observed/expected deaths	SMR (95% CI)
All causes	142/32.8	4.33 (3.67–5.10)
Malignant neoplasms	13/9.1	1.42 (0.83–2.45)
Diseases of the circulatory system	28/8.8	3.19 (2.20–4.62)
Ischaemic heart disease	9/5.0	1.79 (0.93–3.45)
Cerebrovascular diseases	8/2.3	3.45 (1.73–6.90)
Diseases of the respiratory system	38/2.8	13.59 (9.89–18.67)

SMR, standardized mortality ratios; CI, confidence interval.

59 years (10% vs 4% and 0% vs 5% respectively). A study in France in 2014 also reported that the proportions of deaths due to neoplasms was lower in people with CP (7% vs 29%), and the proportion of deaths due to diseases of the respiratory system was higher in people with CP (19% vs 6%) compared to the general population.<sup>8</sup> However, in contrast to the findings of the current study, the proportion of deaths due to diseases of the circulatory system was lower among people with CP (15% vs 29%). The conclusions that can be drawn from these previous studies in England and France are limited as they did not directly compare cause-specific mortality rates between people with CP and the general population. As noted by a reviewer, such studies are particularly prone to bias as they do not account for differences in person-years of exposure between groups, when comparing the proportions of deaths attributed to a given cause. Differences in proportionate cause-specific mortality between groups may therefore reflect issues such as an excess of deaths due to the specific cause in the first group, a deficit in deaths due to other causes in that group, or an excess of deaths due to other causes in the second group. Further, without adjusting for age, sex, and calendar year, differences in cause-specific mortality may also be due to differences in the structure of groups relating to these variables.

In 1999, Strauss et al.<sup>4</sup> directly compared mortality rates using appropriate methods and our findings are largely supportive of this study. Specifically, Strauss et al.<sup>4</sup> reported SMRs of 5.4 and 13.8 for all-cause mortality for people with ‘not severe’ and ‘severe’ CP respectively (severe CP was defined as a ‘condition so substantial that it is exceedingly difficult to find an appropriate placement for the client and/or constant care/supervision is required’). The difference between the SMRs reported by Strauss et al. and those observed in the current study may be because data used by Strauss et al. were obtained from a database of people with CP in California receiving services from the state. As a result, the sample may be biased towards more severely involved individuals. By using primary care data in England, the current study included a cohort that was more likely to be representative of the population of people with CP in England. Although Strauss et al.<sup>4</sup> also reported an increased risk of mortality

due to diseases of the respiratory system among people with CP, they reported much higher SMRs for a range of respiratory diseases including pneumonia and chronic obstructive pulmonary disease (SMRs ranged from 2.3–90.8 for people aged >15y without severe CP). SMRs for ischaemic heart disease and cerebrovascular disease however were very similar to those found in the current study (1.8–4.1). In contrast to the findings of this study, Strauss et al. and a later study using the same Californian data set reported evidence of an increased risk of cancer-related mortality.<sup>4,6</sup>

It should be noted that although we did not find evidence of increased risk of mortality due to ischaemic heart disease and cancer, the effect sizes for these conditions were almost identical to those previously reported for ischaemic heart disease (SMR: 2.2)<sup>4</sup> and for all cancers (1.31, 95% CI 1.14–1.51).<sup>6</sup> The relatively small number of cancer deaths occurring in this cohort resulted in wide CIs and thus, in contrast to previous studies, evidence of increased risk was not observed. However, the direction and magnitude of risk in people with CP was in line with previous findings.

Although there is little research on the risk of mortality due to cardiovascular disease in people with CP, there is a growing evidence base to support increased risk of cardiovascular disease in this population. In the past 3 years, studies have consistently reported an increased risk of myocardial infarction and stroke among people with CP.<sup>17–19</sup> Identification and management of risk factors for cardiovascular disease, including hypertension, overweight/obesity, smoking, and elevated cholesterol levels, is essential to prevention of cardiovascular disease. However, a recent systematic review identified inconsistent evidence regarding the prevalence of risk factors for cardiovascular disease among adults with CP.<sup>20</sup> The current evidence base regarding the prevalence of risk factors among adults with CP is limited by small studies, potentially biased samples, and lack of a comparison group of people without CP that is similar on confounding factors such as age.<sup>20</sup> Therefore, while we may speculate on the causal pathway between CP and cardiovascular disease there is limited evidence to support any hypotheses.

There is also evidence of increased risk of asthma and chronic obstructive pulmonary disease among people with CP, although findings have been mixed to date.<sup>17–19</sup> It is widely acknowledged that the risk of death due to acute respiratory disease is high in CP.<sup>3,5</sup> While our findings support the increased risk of respiratory disease-related mortality in people with CP, we were unable to differentiate between mortality risk due to acute and chronic respiratory disease. The very high relative risk of death due to respiratory disease highlights the importance of vaccination against acute respiratory conditions such as influenza in this population. While CP is a high-risk condition for complications associated with influenza, recognition of this among physicians remains suboptimal and a recent study in the USA indicated that only

approximately 60 per cent of children with CP in the USA were vaccinated, or their parents intended on vaccinating them, against influenza.<sup>21</sup>

As indicated previously, a strength of this study was the use of a cohort identified from a nationally representative data set. We also compared death registrations in people with CP to those in the general population from the same source (ONS). Unlike previous studies conducted in Europe, comparisons between mortality rates in people with and without CP were adjusted for age, sex, and calendar year. Limitations of this study include the relatively small sample, and, in particular, the small number of observed deaths. As a result, it was not possible to explore the risk of specific cardiovascular diseases, respiratory diseases, and cancers, and CIs were wide. We were also unable to examine effect modification by age, severity of motor impairment, or ability to self-feed. Further, it was not possible to describe the distribution of severity of motor impairment in the sample as a measure of severity is not available in the CPRD.

The results of this study add to the evidence base that consistently suggests an increased risk of cardiovascular disease among people with CP.<sup>10</sup> Potential explanations for this increased risk in people with CP include physical

inactivity,<sup>10</sup> poor knowledge of modifiable cardiovascular risk factors,<sup>22</sup> and inadequate access to coordinated services in adulthood.<sup>23</sup> While primary prevention should be the focus of the management of cardiovascular disease, and indeed cancer and chronic respiratory disease,<sup>24</sup> secondary prevention also needs to be examined in people with CP.<sup>10</sup> The increased risk of cardiovascular- and respiratory-related mortality in people with CP may be partly explained by delays in diagnosis and treatment of existing disease. However, as no study has examined the management of these conditions in people with CP,<sup>10</sup> future research is urgently required to explore this further.

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## SUPPORTING INFORMATION

The following additional material may be found online:

**Appendix S1:** Read codes for cerebral palsy.

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