Risk of depression and anxiety in adults with cerebral palsy: A UK-cohort study using GP data.

Short title: Depression, anxiety and cerebral palsy

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Abstract

Importance: Cerebral palsy (CP) is considered a paediatric condition despite most people living into adulthood. Due to this we lack evidence in adults with CP, this includes a paucity of research examining mental health in this population.

Objectives: Determine the risk of depression and anxiety in adults with a diagnosis of CP compared with an age-, sex-, and practice-matched reference group of adults without CP, using primary care data.

Design, setting and participants: Retrospective longitudinal cohort study set in UK primary care. Data were analysed using Cox proportional hazards regression analyses adjusted for chronic conditions and visits to their physician. The study period ran from 1987 to 2015.

Data for 1,705 adults aged 18 or older with CP and 5,115 matched adults who did not have CP were extracted. CP was identified using diagnostic codes, and each person with CP was compared with 3 age, sex and practice matched controls.

Exposure: Diagnosis of CP, with a second analysis accounting for co-morbidity of intellectual disability (ID).

Main outcomes: Time to diagnosis for depression or anxiety following the date of entry into the study in adults with CP (with and without ID) when compared with matched controls.

Results: The mean age of the CP and matched group was 33.3 and 46.8% (n=798) were female. People with CP had an increased adjusted hazard of depression (HR 1.28, 95% CI: 1.09-1.51) and anxiety (HR 1.40, 95% CI: 1.21-1.63) when compared with the matched reference group. When we accounted for ID co-morbidity there were 363 adults with CP who also had ID (mean age 32.1, 47.6% (n=159) female) and 1342 adults with CP who did not have ID (mean age 33.6, 43.8% (n=639) female). Only those people with CP and no co-morbid ID had a higher

risk of incident depression (HR 1.44: 95% CI 1.20-1.72) and anxiety (HR 1.55: 95% CI 1.28-1.87) than their matched controls.

Conclusions: The results demonstrate that adults with CP have an increased risk of depression or anxiety. In particular, our results indicate that this association is driven largely by those individuals with CP with no co-occurring ID. Future work is needed in community-based samples in order to fully elucidate the causal mechanisms driving these associations.

Key points

- Questions: What is the risk of depression and anxiety in adults with cerebral palsy when compared with age, sex and area matched controls?

  Findings: Adults with cerebral palsy have an increased risk of depression and anxiety when compared with age, sex and practice-matched controls. When we also accounted for intellectual disability co-morbidity we found that it was only those adults who had cerebral palsy with no intellectual disability that had an increased risk of depression and anxiety.

  Meaning: Adults with cerebral palsy have a higher risk of developing anxiety and depression than adults who do not have cerebral palsy.

Introduction

Cerebral palsy (CP) is the umbrella term used for a heterogeneous group of etiologies that occur to a developing foetal or infant brain (1). People diagnosed with CP have similar hallmark symptoms including issues with movement, coordination, posture, and balance (1, 2). These motor disturbances can also be co-morbid with other issues such as behavioral disturbance, cognitive difficulties, communication difficulties, sensory impairments, epilepsy, and intellectual disability (ID) (1).It is estimated that CP affects 2-3 in 1,000 live births, and approximately 1 in 400 people in the UK live with CP (3, 4).

Due to the fact that the CP develops and is diagnosed in early childhood (5) it is often considered a paediatric condition. However, CP is a lifelong condition with the majority of children living into adulthood, depending on the severity of the condition and associated physical co-morbidities (6, 7). There is evidence that as people with CP transition into and throughout adulthood, there can be deterioration in physical functioning, and a rise in secondary health conditions (8, 9). The experience of ageing with CP is therefore likely to be linked with different psychological, social and medical issues than those experienced through having CP as a child. However, most evidence on mental health and CP is focused on children (10), which cannot be generalized to adult populations.

Depression and anxiety are two of the most common mental illnesses in the general population (11). and there is substantial evidence that living with a long-term condition or disability is associated with a two-to-three fold increase in the likelihood of being diagnosed with depression (12, 13) or anxiety (14). However, there is relatively little research specifically examining mental health outcomes in adults with CP.

Existing evidence indicates that 20-25% of adults with CP have clinically significant levels of depressive symptoms (15, 16). Furthermore, a recent clinical study in 501 adults with CP from a clinic in the USA found that 39% of patients met criteria for a diagnosis of anxiety

disorder, and 31% met criteria for a diagnosis of major depression (17). A recent paper that compared the prevalence of depression and anxiety in adults with CP to the general population found that adults with CP were more likely to experience depression, but not anxiety, than the general population (18). However, this work was cross-sectional and there is a need for longitudinal work to systematically investigate whether CP is associated with an increased risk of anxiety or depression in adulthood.

However, the association between depression, anxiety and CP could be modified by co-morbid intellectual disability (ID). Approximately a third of people with CP also experience co-morbid ID (2); however, ID has been associated with difficulties correctly identifying common mental illness due to diagnostic overshadowing (19). Diagnostic overshadowing can happen in people with ID because distress (including anxiety and depression) can present as challenging behaviours instead of the symptoms we typically associate with depression and anxiety (20, 21). In other words, the challenging behaviours overshadow the correct diagnosis of mental illness. This could mean that although we might expect the incidence of anxiety and depression to be higher in adults with CP, it is also important to account for the presence of ID.

The aim of this paper was to determine the incidence of depression and anxiety in adults with CP, as compared with age-, sex-, and general practice-matched controls using primary care data from the United Kingdom. We also sought to determine whether the presence of co-morbid ID impacted on the associations between CP and incident depression and anxiety.

Methods

Clinical Practice Research Datalink (CPRD) database

Data for this study was taken from the CPRD primary care database. This database reflects the collection of consultation data from consenting general practices throughout the UK, and it covers 6.9% of the UK population with active data available for 4.4 million people (22).

Previous work has shown the population contained within the CPRD database are representative of the UK population (22). Collected data includes clinical events, prescriptions, referrals and hospital admissions. Formal data collection commenced in 1987 and data for this study was from the period 1 January 1987 to 30 November 2015. CPRD obtained ethical approval from a National Research Ethics Service Committee which allows researchers to access anonymised data for observational studies upon the approval of a protocol to an Independent Scientific Advisory Committee (ISAC).

Participants

Any patient aged 18 or older who had at least one record of CP during the study period, and during a period in which their data was considered research-standard (i.e., their data were determined by CPRD to be of sufficient quality for research assessment), was included as a case of CP. CPRD checks data to ensure it is research standard by determining whether the patient-level data consists of valid registration dates and that the data provided by the practice has been continuous (22).

Diagnoses were identified using Read codes which are alphanumeric codes used in UK healthcare to reference a Read term that captures the reason for consultation (e.g., the Read code F2B..00 refers to the Read term 'Cerebral Palsy') A diagnosis of CP was identified by one of 22 Read codes for CP which were created by the senior investigator (JR) and checked by other CP experts (see Appendix A). The index date, i.e. the start of follow-up, was defined as the latest of: (1) The date that the patient registered with their General Practitioner (GP); (2) The date that their data became research-standard; or (3) The year in which they turned 18. Initially 14,788 patients with CP were identified. Following exclusions based on age (<18 years old, n=2,510), a Read code for CP not occurring within the study period and/or a period when data were research-standard (n=10,038), and potentially inaccurate codes (n=535), a sample of 1,705 patients with CP were included within the main analysis.

Each patient with CP was matched to three patients who did not have CP for age (within ± 3 years), sex and practice. Practice was used as an indicator of area-level socioeconomic status, as CPRD uses area-level deprivation as an indicator of socioeconomic position (23). In total 5,115 matched controls were identified, and these matched controls acted as the reference (comparison) group for our main analyses. The index date for each patient without CP was set as the same date as their respective matched CP case.

In additional analyses, we also examined the impact of ID co-morbidity on the incidence of anxiety and depression in adults with CP. These cases were identified using a list of Read codes provided by the Cambridge primary care unit (24). For these additional analyses, we split the CP group into CP patients with no ID co-morbidity (CPnoID) and CP patients with ID (CP+ID).

Identification of depression and anxiety

Cases of depression and anxiety were identified using the read codes developed by John et al. (25) and the Cambridge Primary Care Unit (24). Where the codes could refer to a possible case of depression (e.g., mood disorders or depression-related symptoms) or anxiety (e.g., worrying) these were only considered this a case of depression where the patient was also given antidepressants and/or anxiolytic medication (see Appendix A for a list of Read codes). We excluded those codes that referred to a history of depression or anxiety, depression or anxiety remission, interim reviews or medication reviews (as we wanted to ascertain the first event of depression and anxiety after the index date). The date of the first event of depression was identified following the index date. Where no event of depression occurred, participants were followed-up until the earliest of the following and treated as censored: transfer out of CPRD, death or end of follow-up period. This was repeated for anxiety.

Identification of ID

Read codes developed by the Cambridge primary care unit (24) were used to identify people with ID. These Read codes included specific conditions associated with ID such as fragile X syndrome and Down's syndrome alongside other synonyms for 'learning disability' and 'intellectual disability' (24).

Potential confounders

As other chronic conditions and GP visits could be linked with an increased likelihood of detecting incident anxiety and depression we adjusted our analyses for these confounders. We used the Read codes proposed by the Cambridge primary care unit (24) to identify the following chronic conditions: Heart disease (myocardial infarction, coronary heart disease and/or arrhythmia); lung disease (chronic obstructive pulmonary disease, chronic bronchitis and/or asthma); pain conditions (four or more prescriptions of pain medication); epilepsy and diabetes. We also identified Read codes for osteoarthritis based on ICD-9 and ICD-10 read terms. Finally we identified the average number of GP visits per year, (0-2 visits per year, 2-11.9 visits per year or ≥12 visits per year). We used 12 visits per year as an indicator for frequent GP consultations as has been done in previous work (26).

For each potential confounder we identified only those cases that occurred before the event date (i.e., depression diagnosis or anxiety diagnosis) or the date of censoring.

Statistical analysis

To ascertain risk we used stratified cox proportional hazards regression for both depression and anxiety as outcomes for the group with CP when compared to the matched reference group. These were firstly run unadjusted and then adjusted for potential confounders.

In our stratified analysis we then re-ran all analyses with the CP group stratified by the presence of co-morbid ID. For these analyses we compared CPnoID and CP+ID with their respective matched reference groups. Prior to running our analyses we checked the assumption

of proportional hazards by plotting scaled Schoenfeld residuals against time for all models, and found this assumption was satisfied. All analyses were conducted using STATA 14.0.

Results

Descriptive data

We present descriptive data pertaining to the sociodemographic and health-related characteristics of the sample in Table 1. The mean age of the sample was 33.3 and 46.8% of both the group with CP and matched controls were female. The data also shows that people with CP had a higher frequency of attending the doctor, a higher frequency of epilepsy and a higher frequency of pain conditions than the matched controls.

Risk of depression

During the follow-up period, there were 1,179 new events of depression following the index date. In total, 867 people from the reference group (17.0%) had a new event of depression over a median of 9.1 (minimum 0.01 to maximum 28.01) years of follow-up. In total, 312 patients with CP (18.3%) had a new event of depression over a median of 5.7 (minimum 0.001 to maximum 27.9) years of follow-up (see Table 3). The unadjusted Cox model indicated that patients with CP had an increased hazard of depression when compared to matched patients without CP (HR 1.43: 95% CI: 1.24-1.64). This association remained significant (HR 1.28: 95% CI 1.09-1.51) after controlling for other chronic conditions and the average number of GP visits (see Table 3).

After stratifying for the presence of co-morbid ID in people with CP, we found that there were 264 (19.6%) new cases of depression in the CPnoID group over a median of 5.2 (minimum 0.05 to maximum 27.9) years of follow-up. However, there were 48 (13.3%) new cases of depression in the CP+ID group over a median of 7.4 (minimum 0.01 to maximum 26.1) years of follow-up. When we conducted Cox regression analysis, stratified according to presence of ID, we found that the CPnoID group had an increased adjusted hazards of incident

depression compared with their matched reference group (adjusted HR 1.44: 95% CI 1.20-1.72) (see Table 4). For both unadjusted and adjusted analyses, the CP+ID group had no difference in their hazard of incident depression when compared to their matched reference group (see Table 4). For Kaplan-Meier plots see Appendix C.

Risk of anxiety

During the follow-up period, there were 958 new events of anxiety after the index date. In total, 697 people from the reference group (13.6%) had a new event of anxiety over a median of 9.5 (minimum 0.01 to maximum 28.0) years of follow-up and 261 patients with CP (15.3%) had a new event of anxiety over a median of 6.0 (minimum 0.003 to 27.9) years of follow-up (see Table 3). The unadjusted hazards ratio indicated an increased risk of anxiety for people with CP when compared with the matched reference group (HR 1.40, 95% CI: 1.21-1.63). This increased risk persisted after controlling for other chronic conditions and the average number of GP visits (HR 1.38: 95% CI 1.15-1.64) (see Table 3).

After stratifying for co-morbid ID, we found that in the CPnoID group there were 217 (16.2%) new cases of incident anxiety over a median of 5.6 (minimum 0.003 to maximum 27.9) years of follow-up (see Table 3). In the CP+ID group, there were 44 (12.2%) new cases of incident anxiety over a median of 7.7 (minimum 0.06 to maximum 26.1) years of follow-up (see Table 3). The Cox regression analysis indicated that the CPnoID group had an increased adjusted hazards of incident anxiety when compared to their matched reference group (HR 1.55: 95% CI 1.28-1.87) (see Table 3). However, the CPnoID group had no difference in their unadjusted or adjusted hazards of experiencing incident anxiety when compared to their matched reference group (see Table 3). For Kaplan-Meier plots see Appendix C.

Sensitivity analysis

As a total of 24 participants within the noCP group also had ID which could affect estimates, we re-ran all analyses excluding these participants from our ID stratified analyses (see

Appendix B). Removal of people with ID from the control group did not have a substantial effect on the results (see Appendix B).

Discussion

Results from this study indicated that people with CP had an increased risk of being diagnosed with depression or anxiety, when compared with a matched control group of adults without CP. These results could have been observed because adults with CP present with many physiological, psychological, social and health-related risk factors that have been shown to be associated with depression and anxiety in the general population such as multimorbidity (27-29), increased pain (30-32), functional limitations (2, 33), noncommunicable diseases (12, 14, 34, 35), difficulties with social relationships (36, 37) and poorer sleep (38, 39). Furthermore, when we examine work that has been conducted in adults with CP depressive symptoms are associated with fatigue (15) and pain (15, 40). However, we need more work to determine why people with CP may have a higher risk of depression and anxiety so that we may develop the evidence-base for mental health interventions in this population.Our results also indicate that ID co-morbidity should be considered when assessing the mental health of adults with CP. We found the risk of depression and anxiety was higher in the adults with CP who did not have ID, compared with the matched reference group. Furthermore, adults with CP and ID had a similar hazards of developing depression and anxiety to the matched reference group. We could have observed these results as previous work suggests that diagnostic overshadowing may lead to an under diagnosis of mental illness among people who have ID (19) due to the fact that distress can present as challenging behaviours (20, 21). Thus, it is possible that GPs may not be as well trained in diagnosing depression and anxiety in these individuals. However, there is also work that has been conducted in populations with ID, indicating that the prevalence of anxiety and depression in people with ID is no different to the general population (21).

While our evidence suggests an increased risk of developing anxiety and depression in adults with CP when compared with adults who do not have CP it should be noted that there was little difference in absolute risk for developing anxiety or depression over the total follow-up period.

This is the first study to examine the risk of depression and anxiety in adults with CP to adults who do not have CP using a population-based cohort. The results support previous work that shows a relatively high frequency of depression and anxiety in individuals with CP (15, 17).

However, there are limitations that should be borne in mind. Due to the nature of the population examined and the reliance on the presence of diagnostic codes to define outcomes, there is a possibility that any observed associations are underestimated as previous work suggests depression and anxiety diagnoses in primary care may be underestimated (41, 42). This could also explain why the rates of depression and anxiety we observed in CP for this study were lower than other studies have previously reported (17, 18). Furthermore, CP is an umbrella term used to describe heterogeneous etiologies, however we could not account for the severity of issues associated with CP. These include gross motor function, communication issues, subtypes of motor abnormality, and fatigue. Future work should provide more insight into how CP-specific issues might be associated with mental health. In addition, the measure of pain conditions that we had within this study relied only on medications.

There are also additional caveats that should be borne in mind when interpreting these data. Depression and anxiety are both considered chronic conditions that typically have their first onset in adolescence or early adulthood (43), therefore it is plausible to assume that some people may have had diagnoses of depression and anxiety prior to the index date for this study. In future work it could be interesting to look at the lifecourse of mental illness in people with CP, looking at people from adolescence through to older age.

In conclusion, this work provides evidence that adults with CP have an increased risk of developing depression and anxiety. Furthermore, co-morbidity of ID is an important effect modifier that should be considered when examining the mental health of adults with CP. There is a need for more work to elucidate the causal mechanisms of poor mental health in adults with CP so that we may develop targeted interventions.

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Table 1: Characteristics of participants

		No CP (n=5,115)	*CP (n=1,705)*	*CPnoID (n=1342)*	*CP+ID (n=363)*
Age	***<30***	2631 (51.44%)	877 (51.44%)	691 (51.49%)	186 (51.24%)
	30-39	1008 (19.71%)	335 (19.71%)	252 (18.78%)	84 (23.14%)
	40-49	669 (13.08%)	223 (13.08%)	172 (12.82%)	51 (14.05%)
	50-59	405 (7.92%)	135 (7.92%)	108 (8.05%)	27 (7.44%)
	>=60	402 (7.86%)	134 (7.86%)	119 (8.87%)	15 (4.13%)
Sex	***Male***	2721 (53.20%)	907 (53.20%)	703 (52.83%)	204 (56.20%)
	Female	2394 (46.80%)	798 (46.80%)	639 (47.62%)	159 (43.80%)
Region	***North***	1419 (27.74%)	473 (27.74%)	349 (26.01%)	124 (34.16%)
	Midlands	1809 (35.37%)	603 (35.37%)	498 (37.11%)	105 (28.93%)

	South	1761 (34.43%)	587 (34.43%)	459 (34.02%)	128 (35.26%)
	Northern Ireland	126 (2.46%)	42 (2.46%)	36 (2.68%)	6 (1.65%)
Average GP visits per year	***0-1.9 per year***	715 (14%)	133 (7.83%)	123 (9.20%)	10 (2.76%)
	2-11.9 per year	4035 (78.99%)	1178 (69.33%)	956 (71.50%)	222 (61.33%)
	≥ 12 per year	358 (7.01%)	388 (22.84%)	258 (19.30%)	130 (35.91%)
Presence of:	***Depression***	867 (16.95%)	312 (18.30%)	263 (19.60%)	49 (13.50%)
	Anxiety	697 (13.63%)	261 (15.31%)	216 (16.10%)	45 (12.40%)
	Diabetes	218 (4.26%)	55 (3.23%)	47 (3.50%)	14 (3.86%)
	Heart disease	584 (11.42%)	160 (9.38%)	165 (12.30%)	20 (5.51%)
	Osteoarthritis	320 (6.26%)	87 (5.10%)	90 (6.71%)	15 (4.13%)
	Epilepsy	49 (0.96%)	354 (20.76%)	216 (16.10%)	155 (42.70%)
	Lung disease	379 (7.41%)	147 (8.62%)	143 (10.66%)	26 (7.16%)
	Pain conditions	238 (4.65%)	166 (9.74%)	179 (13.34%)	23 (6.34%)

This table presents the distribution of the sociodemographic and health-related characteristics of patients within the sample. The CP column presents data for all people with CP in the sample, the CPno ID and CP+ID columns represent people from the CP column stratified for the presence of ID.

CPnoID: Cerebral Palsy with no co-morbid ID
CP+ID: Cerebral Palsy with co-morbid ID.

Table 2: Incidence of depression and anxiety in people with Cerebral Palsy (n=1705) compared with age, sex and practice-matched controls (n=5115).

		Events n (%)	*Person years in 10,000s*	*Incidence per 10,000 person years*	*Unadjusted HR (95% CI) and p-value*	*Adjusted HR †(95% CI) and p-value*
Depression	***No CP***	867 (16.95%)	49.93	0.017 (0.016-0.019)	1	1
	CP	312 (18.30%)	12.64	0.025 (0.022-0.028)	1.43 (1.24-1.64), *p<.001*	1.28 (1.09-1.51), *p=.003*
Anxiety	***No CP***	697 (13.63%)	51.67	0.013 (0.013-0.015)	1	1
	CP	261 (15.31%)	12.93	0.020 (0.018-0.023)	1.40 (1.21-1.63), *p<.001*	1.38 (1.15-1.64), *p<.001*

† Adjusted for baseline (i.e., pre-depression or pre-anxiety diagnosis) diagnosis of diabetes, heart disease, lung disease, osteoarthritis, epilepsy, pain conditions and GP visits per year.

Table 3: Incidence of depression and anxiety in people with CP with and without co-morbid ID

		Events n (%)	*Person years in 10,000s*	*Incidence per 10,000 person years*	*Unadjusted hazards ratio (95% CI) and p-value*	*Adjusted hazards ratio (95% CI)* † and p-value
Depression CPnoID	***Matched reference group***	687 (17.04%)	39.32	0.017 (0.016-0.019)	1	1
	CPnoID	264 (19.64%)	9.55	0.028 (0.025-0.031)	1.59 (1.36-1.85), p<.001	1.44 (1.20-1.72), p<.001
Depression CP+ID	***Matched reference group***	180 (16.62%)	10.61	0.017 (0.015-0.020)	1	1
	CP+ID	48 (13.30%)	3.10	0.015 (0.012-0.021)	0.92 (0.66-1.29), p=.66	0.68 (0.43-1.07), p=.09
Anxiety CPnoID	***Matched reference group***	542 (13.44%)	40.72	0.013 (0.012-0.014)	1	1
	CPnoID	217 (16.15%)	9.79	0.022 (0.019-0.025)	1.57 (1.32-1.85), p<.001	1.55 (1.28-1.87), p<.001
Anxiety CP+ID	***Matched reference group***	155 (14.31%)	10.94	0.014 (0.012-0.017)	1	1
	CP+ID	44 (12.19%)	3.15	0.014 (0.010-0.019)	0.92 (0.65-1.30), p=.65	0.77 (0.48-1.25), p=.29

† Adjusted for baseline (i.e., pre-depression or pre-anxiety diagnosis) diagnosis of diabetes, heart disease, lung disease, osteoarthritis, epilepsy, pain conditions and GP visits per year.

CPnoID: Cerebral Palsy with no co-morbid ID
CP+ID: Cerebral Palsy with co-morbid ID.

Each CP group was compared to their respective age, sex and practice matched reference group. CPnoID N=1342 and their respective matched group N=4026. CP+ID N=363 and their respective matched group N=1089.

Appendix A

Read codes and associated Read terms used to define Cerebral Palsy

Read code	Read term
F23y400	Ataxic diplegic cerebral palsy
F23y000	Ataxic diplegic cerebral palsy
F137.11	Athetoid cerebral palsy
F137000	Athetoid cerebral palsy
F2B..00	Cerebral palsy
F2Bz.00	Cerebral palsy NOS
F230100	Cerebral palsy with spastic diplegia
F23..00	Congenital cerebral palsy
F23y300	Dyskinetic cerebral palsy
F23..12	Infantile cerebral palsy
F23y200	Spastic cerebral palsy
F230111	Spastic diplegic cerebral palsy
F2B1.00	Spastic hemiplegic cerebral palsy
F2B0.00	Spastic quadriplegic cerebral palsy
F23yz00	Other infantile cerebral palsy NOS
Fyu9000	[X]Other infantile cerebral palsy
F23y.00	Other congenital cerebral palsy
F23y100	Flaccid infantile cerebral palsy
F2By.00	Other cerebral palsy
Fyu9.00	[X]Cerebral palsy and other paralytic syndromes
F23z.00	Congenital cerebral palsy NOS
F23..11	Congenital spastic cerebral palsy
F23y600	Choreoathetoid cerebral palsy

Read codes and associated Read terms used to define Depression

Read Code	Read term
Depression	
Eu32700	[X] Major depression, severe without psychotic symptoms
Eu32200	[X] Severe depressive episode without psychotic symptoms
Eu32213	[X] Single episode vital depression without psychotic symptoms
Eu33214	[X] Vital depression, recurrent without psychotic symptoms
Eu3y111	[X] Recurrent brief depressive episodes
E113700	Recurrent depression
E2B1.00	Chronic depression
E113200	Recurrent major depressive episodes, moderate
E113.00	Recurrent major depressive episode
Eu33100	[X] Recurrent depressive disorder, current episode moderate
E112.11	Agitated depression
E135.00	Agitated depression
Eu32.11	[X] Single episode of depressive reaction
E112200	Single major depressive episode, moderate
Eu33211	[X] Endogenous depression without psychotic symptoms
Eu32.13	[X] Single episode of reactive depression
E112300	Single major depressive episode, severe, without psychosis
E112000	Single major depressive episode, unspecified
Eu33200	[X] Recurrent depressive disorder current episode severe without psychotic symptoms
E112.13	Endogenous depression first episode
E112.14	Endogenous depression
Eu33212	[X] Major depression, recurrent without psychotic symptoms
Eu32212	[X] Single episode major depression without psychotic symptoms
Eu32211	[X] Single episode agitated depression without psychotic symptoms
Eu33000	[X] Recurrent depressive disorder, current episode mild
E113700	Recurrent depression
Eu33.11	[X] Recurrent episodes of depressive reaction
E11y200	Atypical depression disorder
E113100	Recurrent major depression episodes, mild
Eu32400	[X] Mild depression
Eu32z13	[X] Prolonged single episode of reactive depression
E113.11	Endogenous depression - recurrent
E112.12	Endogenous depression first episode
E112.00	Single major depression episode
E290.00	Brief depressive reaction
Eu32y11	[X] Atypical depression
Eu33.13	[X] Recurrent episodes of reactive depression
E113300	Recurrent major depressive episodes, severe, no psychosis
Eu33.12	[X] Recurrent episodes of psychogenic depression

Eu32.12	[X] Single episode of psychogenic depression
Eu32600	[X] Major depression, moderately severe
Eu33.00	[X] Recurrent depressive disorder
Eu33z00	[X] Recurrent depressive disorder, unspecified
E291.00	Prolonged depressive reaction
Eu32500	[X] Major depression, mild
E112100	Single major depressive episode, mild
Eu32000	[X] Mild depressive episode
Eu32.00	[X] Depressive episode
Eu32z00	[X] Depressive episode, unspecified
E2B..00	Depressive disorder NEC
1B17.00	Depressed
2257	o/e - depressed
1B1U.11	Depressive symptoms
1B1U.00	Symptoms of depression
1B17.11	c/o - feeling depressed
1BT..00	Depressed mood
1JJ..00	Suspected depression
Depression with psychosis	
Eu32800	[X] Major depression, severe with psychotic symptoms
Eu32313	[x] Single episode of psychotic depression
Eu33315	[X] Recurrent severe episodes of psychotic depression
E113400	Recurrent major depressive episodes, severe, with psychosis
Eu33300	[X] Recurrent depressive disorder current episode severe with psychotic symptoms
E112400	[X] Single major depressive episode, severe, with psychosis
Eu33314	[X] Recurrent severe episodes/psychogenic depressive psychosis
Eu33316	[X] Recurrent severe episodes/reactive depressive psychosis
Eu32311	[X] Single episode of major depression and psychotic symptoms
Eu32312	[x] Single episode of psychogenic depressive psychosis
Eu32314	[X] Single episode of reactive depressive psychosis
E11..12	Depressive psychoses
Eu32300	[X] Severe depressive episode with psychotic symptoms
Eu33311	[X] Endogenous depression with psychotic symptoms
E130.00	Reactive depressive psychosis
E130.11	Psychotic reactive depression
Eu33313	[X] Recurrent severe episodes/major depression + psychotic symptoms
Depression other or NOS	
E113z00	Recurrent major depressive episode nos
Eu33y00	[X] Other recurrent depressive disorders
Eu32y00	[X] Other depressive episodes
E113000	Recurrent major depressive episodes, unspecified
E290z00	Brief depressive episode nos
Eu32y12	[X] Single episode of masked depression NOS

E11z200	Masked depression
Eu33z11	[X] Monopolar depression NOS
Eu32z14	[X] Reactive depression NOS
E112z00	Single major depression episode NOS
Eu32100	[X] Moderate depressive episode
Eu32z11	[X] Depression NOS
Eu32z12	[X] Depressive disorder NOS
E112.11	agitated depression
Eu32211	[x]single episode agitated depression w'out psychotic symptoms
Dysthymia	
Eu34100	Dysthymia
Eu34112	[X] Depressive personality disorder
E211200	Depressive personality disorder
Eu34111	[X] Depressive neurosis
Eu34113	[X] Neurotic depression
E204.00	Neurotic depression reactive type
Mixed depression anxiety	
Eu41200	[X]Mixed anxiety and depressive disorder
Eu41211	[X]Mild anxiety depression
E200300	Anxiety with depression
Eu34114	[X] Persistant anxiety depression
Secondary depression	
E204.11	Postnatal depression
Eu53011	[X] Postnatal depression NOS
Eu32B00	[X] Antenatal depression
E001300	Presenile depression with dementia
E002100	Senile dementia with depression
Eu53012	[X] Postpartum depression nos
Eu02z16	[X] Senile dementia, depressed or paranoid type
E002.00	Senile dementia with depressive or paranoid features
R007z13	[d] postoperative depression
E002z00	Senile dementia with depressive or paranoid features NOS
62T1.00	Puerperal depression
E004300	Arteriosclerotic dementia with depression
Eu20400	[x] Post-schizophrenic depression
E02y300	Drug-induced depressive state
Eu92000	[X] Depressive conduct disorder
Eu33.15	[X] SAD- seasonal affective disorder
E118.00	Seasonal affective disorder
Eu33.14	[X] Seasonal depressive disorder
Therapy	
8CAa.00	Patient given advice about management of depression
8HHq.00	Referral for guided self-help for depression

Drugs used to identify possible depression (to be considered a case of depression patients were required to also have one of the read codes indicative of possible depression)

Antidepressants		
		Dosulepin
		Imipramine
		Lofepramine
		Nortriptyline
		Trimipramine
		Amoxapine
		Dothiepin
		Maprotiline
		Mianserin
		Trazadone
Antidepressants (MAOIs)		
		Phenelzine
		Isocarboxazid
		Tranlcypromine
		Moclobemide
Antidepressant (SSRI)		
		Citralopram
		Fluoxetine
		Fluvoxamine
		Paroxetine
		Sertraline
		Escitalopram
Antidepressant (other)		
		Flupentixol
		Mirtazapine
		Reboxetine
		Venlafaxine
		Tryptophan
		Agomelatine
		Duloxetine

Read codes and associated Read terms used to define possible depression.

Read code	Read term
1BT..11	Low mood
1B1J.11	Emotional upset
16ZB100	feeling low or worried

7899	o/e - distressed
E205.11	nervous exhaustion
E20z.11	nervous breakdown
E290011	bereavement reaction
E290000	Grief reaction
8HHK.00	referral to bereavement counsellor
IBT..12	sad mood
1BT..11	Low mood
Eu3z.00	[X] Unspecified mood affective disorder
Eu05300	[X] Organic mood [affective] disorders
Eu34z00	[X] Persistant mood affective disorder, unspecified
Eu34.00	[X] Persistant mood affective disorders
Eu34y00	[X] Other persistant mood affective disorders
Eu3..00	[X] Mood - affective disorders
Eu3y.00	[X] Other mood affective disorders
Eu3y100	[X] Other recurrent mood affective disorders
Eu3y000	[X] Other single mood affective disorders
Eu3yy00	[X] Other specified mood affective disorders
1BO..00	Mood swings

Read codes and associated Read terms used to define Anxiety Disorders

Anxiety disorders were defined as generalised anxiety disorder, mixed depression and anxiety disorder, panic disorder or phobias. As obsessive-compulsive disorders and post-traumatic and acute stress disorders are no longer considered anxiety disorders within the DSM-V we opted to exclude these events as cases of anxiety.

Read code	Read term
Mixed depression anxiety	
Eu41200	[X]Mixed anxiety and depressive disorder
Eu41211	[X]Mild anxiety depression
E200300	Anxiety with depression
Eu34114	[X] Persistant anxiety depression
Anxiety disorder diagnoses	
Eu41.00	[x] other anxiety disorders
Eu40y00	[x]other phobic anxiety disorders
Eu41000	[x]panic disorder [episodic paroxysmal anxiety]
Eu40012	[x] panic disorder with agoraphobia
1B1V.00	c/o - panic attack
Eu41011	[x] panic attack
225J.00	o/e - panic attack
E200111	panic attack
Eu41100	[x]generalized anxiety disorder
Eu41300	[X]Other mixed anxiety disorders
Eu41y00	[X]Other specified anxiety disorders
Eu41z00	[x]anxiety disorder, unspecified
Eu05400	[x]organic anxiety disorder
E2000000	Anxiety state unspecified
Eu41113	[x] anxiety state
E200100	panic disorder
Eu41100	[X] Generalized anxiety disorder
E200200	Generalised anxiety disorder
Eu41111	[x] anxiety neurosis
E200400	Chronic anxiety
E200500	Recurrent anxiety
E200.00	anxiety states
E200z00	anxiety state nos
Eu41z11	[x] anxiety nos
E292000	Separation anxiety disorder
Eu93000	[x] separation anxiety disorder to childhood
E2D0000	childhood and adolescent overanxiousness disturbance
E2D0.00	disturbance of anxiety and fearfulness childhood/ adolescent
E2D0z00	disturbance anxiety and fearfulness childhood/adolescent nos
Eu93y12	[x] childhood overanxious disorder

Eu41112	[x] anxiety reaction
1B13.00	anxiousness
2258	O/E - anxious
1B13.12	anxious
8G94.00	anxiety management training
8HHp.00	referral for guided self-help for anxiety
Z481.00	phobia counselling
8CAZ000	patient given advice about management of anxiety
8G52.00	antiphobic therapy
1B13.11	anxiousness - symptom
Z4I7.00	acknowledging anxiety
Z4I7100	recognising anxiety
Eu41012	[x]panic state
Eu41112	[x] anxiety reaction
Phobias	
Eu40000	[x]agoraphobia
Eu40011	[x]agoraphobia without history of panic disorder
E202100	agoraphobia with panic attacks
E202200	agoraphobia without mention of panic attacks
Eu40200	[x] specific (isolated) phobias
Eu40214	[x] simple phobia
E202700	animal phobia
E202C00	dental phobia
Eu40212	[x]animal phobias
E28z.12	flying phobia
E202A00	Fear of flying
E202E00	Fear of pregnancy
Eu40213	[x] claustrophobia
E202800	claustrophobia
Eu40300	[x]needle phobia
E202600	acrophobia
E202D00	Fear of death
Eu40100	[x]social phobias
E202400	social phobia, fear of public speaking
E202B00	cancer phobia
E202300	social phobia, fear of eating in public
E202500	social phobia, fear of public washing
E202.11	social phobic disorders
Eu93200	[x] social anxiety disorder of childhood
Eu93100	[x] phobic anxiety disorder of childhood
Eu45215	[x]nosophobia
Eu40211	[x] acrophobia
E202600	acrophobia
E202000	Phobia

Eu40z11	[x]phobia nos
E202.00	phobic disorders
E202z00	phobic disorder nos
E202.12	phobic anxiety
Eu40z00	[x] phobic anxiety disorder, unspecified
E202000	Phobia unspecified
Eu40y00	[x] other phobic anxiety disorders
Eu40.00	[x] phobic anxiety disorders
E292000	separation anxiety disorder
Eu40z12	[x] phobic state nos

Drugs used to identify possible anxiety (to be considered a case of anxiety patients were required to also have one of the read codes indicative of possible anxiety)

Anxiolytics		
		Diazepam
		Alprazolam
		Bromazepam
		Chlordiazepoxide
		Chlorezanone
		Clobazem
		Clorazepate dipotassium
		Hydroxyzine hcl (anxiolytic)
		Ketazolam - discontinued
		Lorazepam (anxiolytic)
		Medazepam - discontinued
		Meprobamate
		Oxazepam
SSRIs		Citralopram
		Fluoxetine
		Fluvoxamine
		Paroxetine
		Sertraline
		Escitalopram

Read codes and associated Read terms used to define possible anxiety.

Read code	**Read term**
1B12.00	Nerves' - nervousness
R2y2.00	(d) nervousness
R2y2.	O/E nervous
1B12.12	tension - nervous
R2y2.12	[d] nervous tension
E205.11	nervous exhaustion
E20z.11	nervous breakdown
1B1..00	general nervous symptoms
1B1Z.00	general nervous symptoms nos
2253	o/e - distressed
16ZB100	feeling low or worried
1BK..00	worried

Appendix B

Risk of depression and anxiety in people with CP with and without co-morbid ID (excluding all people without CP who had a diagnosis of ID, n=24).

		Events n (%)	*Person years in 10,000s*	*Incidence per 10,000 person years*	*Unadjusted hazards ratio (95% CI) and p-value*	*Adjusted hazards ratio (95% CI)* † and p-value
Depression CPnoID	***Matched reference group***	684 (17.02%)	39.22	0.017 (0.016-0.019)	1	1
	CPnoID	264 (19.64%)	9.55	0.028 (0.025-0.031)	1.59 (1.36-1.85), p<.001	1.43 (1.20-1.71), p<.001
Depression CP+ID	***Matched reference group***	177 (16.50%)	10.54	0.017 (0.014-0.019)	1	1
	CP+ID	48 (13.30%)	3.10	0.015 (0.012-0.021)	0.92 (0.66-1.28), p=.63	0.69 (0.43-1.09), p=.11
Anxiety CPnoID	***Matched reference group***	540 (13.44%)	40.61	0.013 (0.012-0.014)	1	1
	CPnoID	217 (16.15%)	9.79	0.022 (0.019-0.025)	1.57 (1.33-1.86), p<.001	1.56 (1.28-1.88), p<.001
Anxiety CP+ID	***Matched reference group***	152 (14.17%)	10.87	0.014 (0.012-0.016)	1	1
	CP+ID	44 (12.19%)	3.15	0.014 (0.010-0.019)	0.93 (0.65-1.31), p=.66	0.79 (0.48-1.27), p=.33

† Adjusted for baseline (i.e., pre-depression or pre-anxiety diagnosis) diagnosis of diabetes, heart disease, lung disease, osteoarthritis, epilepsy, pain conditions and GP visits per year.

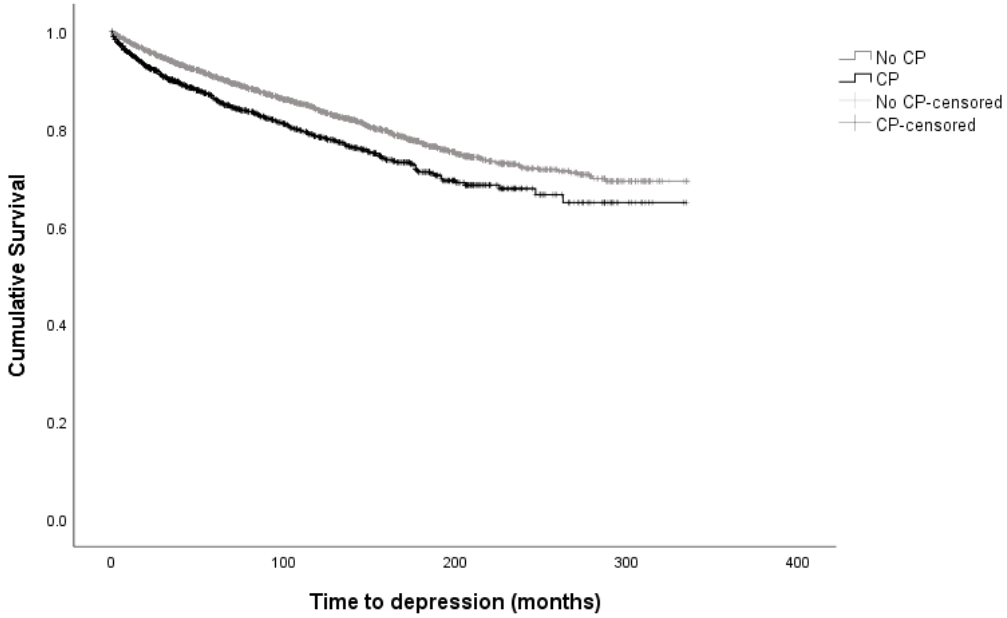
CPnoID: Cerebral Palsy with no co-morbid ID
CP+ID: Cerebral Palsy with co-morbid ID.

Each CP group was compared to their respective age, sex and practice matched reference group. CPnoID N=1342 and their respective matched group N=4026. CP+ID N=363 and their respective matched group N=1089.

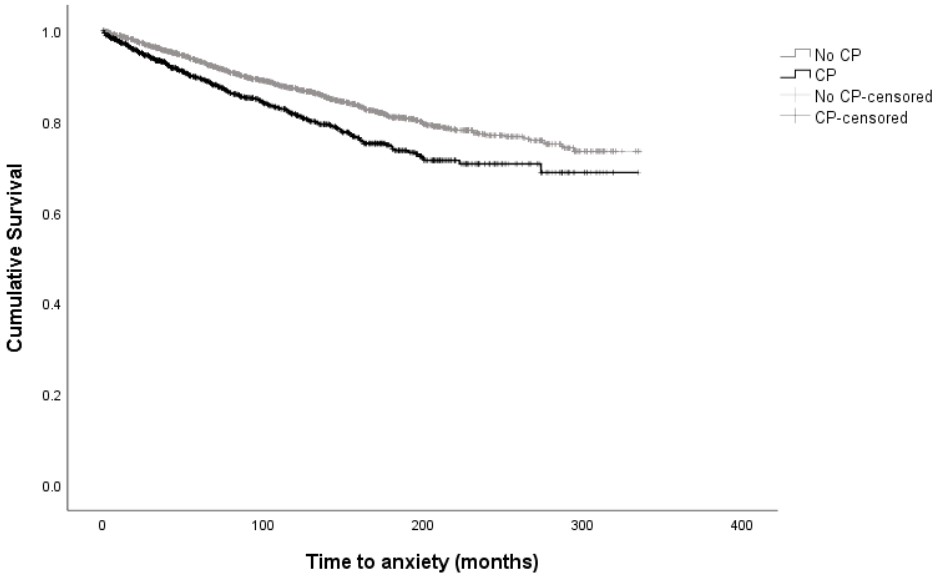
Appendix C: Kaplan Meier survival plots

Comparison of all people with CP (n=1,705) and all matched controls (n=5,115)

Graph i: Time to depression for people with CP and matched-controls

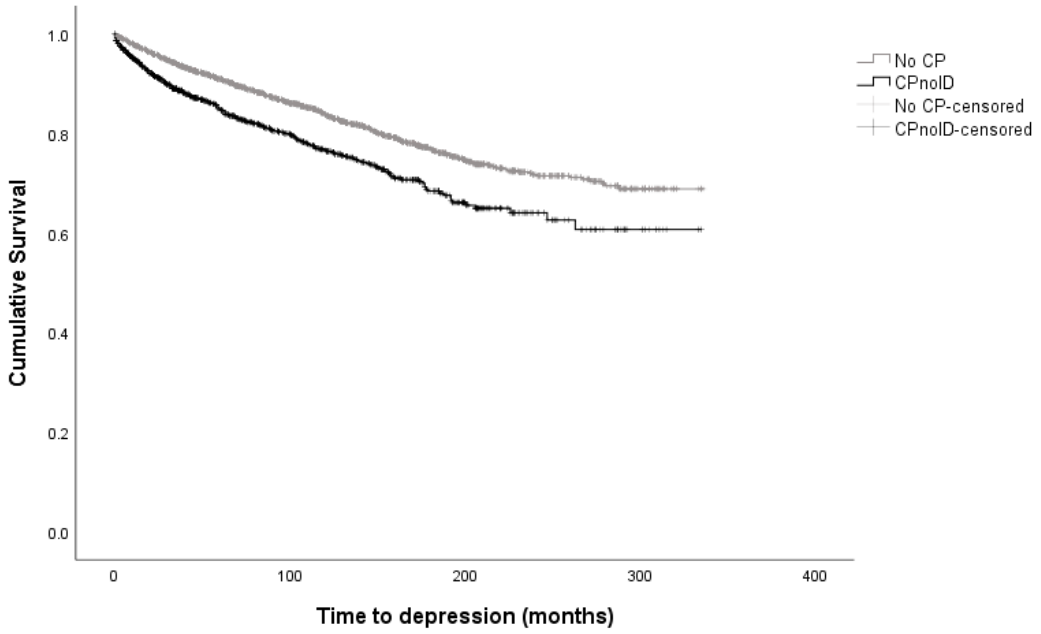


Graph ii: Time to anxiety for people with CP and matched-controls

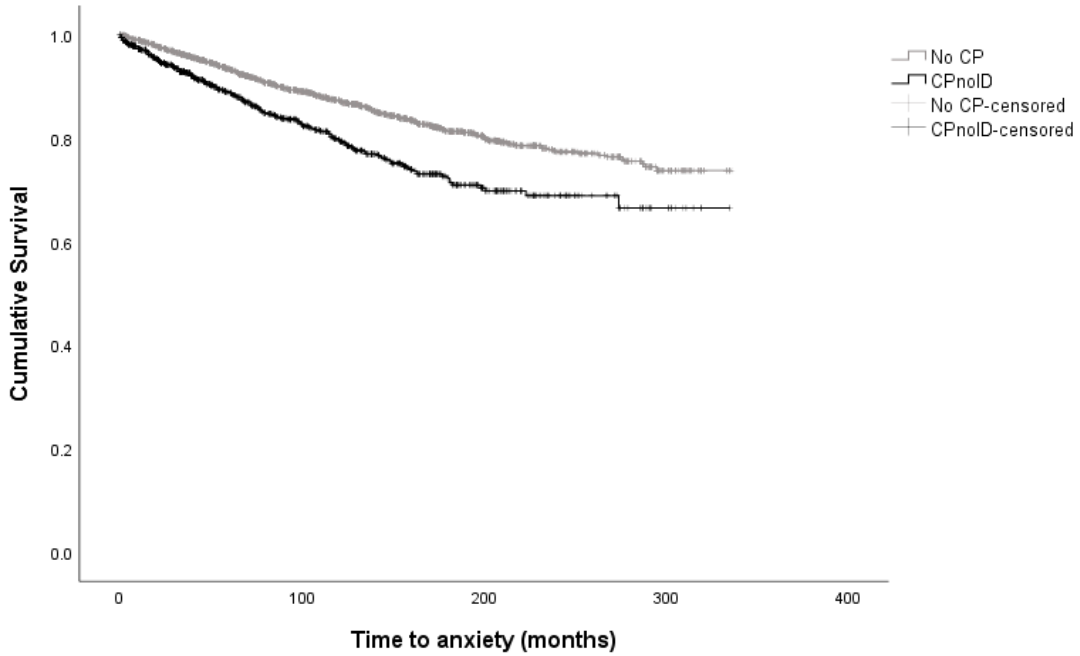


Comparison of CPnoID (n=1,342) with respective matched controls (n=4,026)

Graph iii: Time to depression for people with CPnoID and respective matched-controls

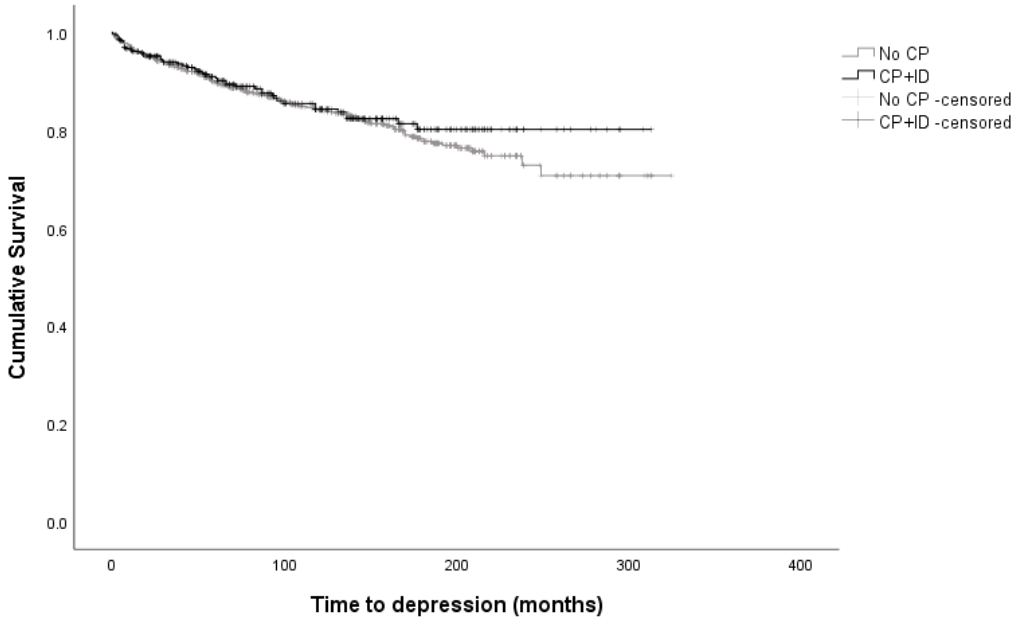


Graph iv: Time to anxiety for people with CPnoID and respective matched-controls



Comparison of CP+ID (n=363) with respective matched controls (n=1,089)

Graph v: Time to depression for people with CP+ID and respective matched-controls



Graph vi: Time to anxiety for people with CP+ID and respective matched-controls