Young adult cognitive ability and subsequent major depression in a cohort of 666,804 Danish men

Christensen, Gunhild Tidemann; Rozing, Maarten Pieter; Mortensen, Erik Lykke; Christensen, Kaare; Osler, Merete

Published in:
Journal of Affective Disorders

DOI:
10.1016/j.jad.2018.04.035

Publication date:
2018

Document version:
Accepted manuscript

Document license:
CC BY-NC-ND

Citation for published version (APA):

Go to publication entry in University of Southern Denmark's Research Portal

Terms of use
This work is brought to you by the University of Southern Denmark. Unless otherwise specified it has been shared according to the terms for self-archiving. If no other license is stated, these terms apply:

- You may download this work for personal use only.
- You may not further distribute the material or use it for any profit-making activity or commercial gain.
- You may freely distribute the URL identifying this open access version.

If you believe that this document breaches copyright please contact us providing details and we will investigate your claim. Please direct all enquiries to puresupport@bib.sdu.dk

Download date: 16. Mar. 2024
Highlights
- A cohort of 666,804 men was followed from young adulthood until late mid-life
- Lower cognitive ability was associated to higher risk of adult major depression
- The association was stronger for single depressive episodes with early-onset
- The association did not differ according to MD severity
- The influence of cognitive ability on re-occurrence was less strong
- Premorbid cognitive ability should be a part of the depression risk assessment
Title: Young adult cognitive ability and subsequent major depression in a cohort of 666,804 Danish men

Gunhild Tidemann Christensen¹,²,³,⁴, Maarten Pieter Rozing⁵,⁶, Erik Lykke Mortensen¹,⁴,⁵, Kaare Christensen²,⁴, Merete Osler³,⁴,⁶

1. Department of Public Health, Section of Social Medicine, University of Copenhagen, Øster Farimagsgade 5, Copenhagen K 1014, Denmark
2. Department of Public Health, Unit of Epidemiology, Biostatistics, and Biodemography, University of Southern Denmark, J. B. Winsløws Vej 9B, Odense C 5000, Denmark
3. Center for Clinical Research and Prevention, Bispebjerg and Frederiksberg Hospital, Capital Region, Copenhagen, Denmark
4. Danish Aging Research Center, Department of Public Health, University of Southern Denmark, Denmark
5. Center for Healthy Aging, University of Copenhagen, Denmark
6. Department of Public Health, Section of Epidemiology, University of Copenhagen, Øster Farimagsgade 5, Copenhagen K 1014, Denmark

Corresponding author: Gunhild Tidemann Christensen, email: guch@sund.ku.dk, address: Department of Public Health, Section of Social Medicine, University of Copenhagen, Øster Farimagsgade 5, PO Box 2099, Copenhagen K 1014, Denmark

Abstract

Background: Early life cognitive ability (CA) might influence the risk of developing major depression (MD). The aim was to investigate the association between young adult CA and subsequent MD in relation to different MD disease characteristics.

Methods: Information on CA was assessed at conscription board examinations 1957-1984 (mean age 19 years) and information on MD was based on hospital diagnosis retrieved from Danish Patient registers 1969-2015. Associations between CA and MD were examined using Cox regression analyses.
Results: A total of 666,804 men were followed and 25,841 (3.9%) developed MD during a mean follow-up of 40.8 years. Lower CA was associated with an increased risk of incident MD. The association was stronger for early-onset (<60 years) (HR_{per1SDdecrease}=1.23; 95%CI:1.21,1.24) compared to late-onset (≥60 years) MD (HR_{per1SDdecrease}=1.14; 95%CI:1.11,1.16), but CA was not related to number of depressive episodes. The association was stronger for single depressive episodes (HR_{per1SDdecrease}=1.21; 95%CI:1.19,1.23) compared to recurrent depression (HR_{per1SDdecrease}=1.13; 95%CI:1.09,1.16), while the strength of the association did not differ according to MD disease severity (ICD10: mild, moderate, and severe depression).

Limitations: The study sample only included men and only MD cases diagnosed at hospital were included which limits the generalizability.

Conclusion: Low CA could be a risk factor for especially early onset MD in men, whereas the influence of CA on re-occurrence seems less strong. Lower pre-morbid CA increases the risk of MD and should therefore be part of the depression risk assessment in clinical practice.

Keywords: Depression, Cognitive ability, Cohort study

1 Background

Low cognitive ability (CA) early in life could be a risk factor for the development of major depression (MD) in adulthood as several potential mechanisms link CA and MD. According to the stress-vulnerability model the risk of MD is increased due to interaction between intrinsic vulnerability (determined by genetic profile and personality) and exposure to stressors for MD (Schaakxs et al., 2017). CA is a stable mental characteristic, which is likely to be an important determinant of exposure to stressors and the ability to cope with stress (Gottfredson, 2004b; Neisser et al., 1996). Early life CA influences later life educational and occupational success (Gottfredson, 2004a; Neisser et al., 1996) and may thus indirectly influence exposure to stressors associated with socioeconomic position, such as unemployment and financial hardship. Moreover, early life CA has been associated to a number of health-related behaviors (e.g. smoking, physical activity, and alcohol consumption) (Batty et al., 2006, 2007a; Batty et al., 2007b, c) and chronic diseases (e.g. stroke, coronary heart disease, and type 2 diabetes) (Batty et al., 2005; Hart et al., 2004; Hemmingsson et al., 2007; Modig Wennerstad et al., 2010; Mottus et al., 2013) which are considered risk factors for developing depression (Lopresti et al., 2013). More speculatively,
theories of cognitive reserve consider CA to be an indicator of individual differences in brain structure (e.g. density of neuronal synapses) and function (e.g. processing speed) (Koenen et al., 2009). Thus, having a high CA, as an indicator of a high cognitive reserve, is hypothesized to buffer the impact of stressors, potentially through neuromodulation of the serotonin system (Barnett et al., 2006) and thereby influence the risk of MD.

A number of studies have investigated the association between CA assessed in childhood or young adulthood and adult MD (assessed by structured diagnostic interviews or hospital diagnosis) or depressive symptoms. Most studies have found that low CA was associated with higher risk of developing MD (Gale et al., 2010; Gale et al., 2008; Koenen et al., 2009; Sorensen et al., 2012; Urfer-Parnas et al., 2010; Zammit et al., 2004), whereas two studies found no association for men (Hatch et al., 2007; Mortensen et al., 2005) and one study found a negative association with low CA in young adulthood being associated with a reduced risk of being hospitalized with MD (Osler et al., 2015). However, most of the previous studies have included relatively few MD cases and have focused on multiple psychiatric disorders rather than providing a more detailed analysis of different characteristics of MD such as age at onset, diagnostic subtype, and severity of the disorder.

Only three of the studies have explored the association between CA and different MD characteristics. One study found an inverse association between low childhood CA and having met the criteria for depression at two or more assessments (Koenen et al., 2009). Another study found low CA to be related to a higher number of hospitalizations with MD (Gale et al., 2010), while no association was found between CA and age at onset (followed from age 18 to 53 years), number of admissions or duration of hospitalization in the third study (Zammit et al., 2004). Thus, knowledge on how early life CA influences MD and the association between CA and different MD characteristics is limited and inconsistent. Moreover, low CA could influence a person’s ability to cope with stressors negatively and may also affect the frequency and amount of stress that a person is exposed to. Thus, CA could be inversely associated with the number of depressive episodes experienced and the association between CA and MD might be stronger for recurrent depression as compared to single depressive episodes and the more severe the depressive episode. Investigating these characteristics remains an important issue because it might contribute to the understanding of the mechanisms behind MD.

Another important characteristic to explore when investigating MD is the age of onset. Studies suggest that depression with an onset early in life (early-onset depression (EOD)) is etiologically different from depression with an onset later in life (after age 60) (late-onset
depression (LOD)) and the association between CA and MD could differ according to age at onset. Based on twin studies MD is overall considered to be moderately heritable (Goltser-Dubner et al., 2010), but a higher rate of family history has been observed in EOD patients compared to LOD patients suggesting that EOD has a stronger genetic underpinning than LOD (Goltser-Dubner et al., 2010; Janssen et al., 2006). LOD is more associated with vascular damage, neurodegeneration and somatic morbidity (Janssen et al., 2006). The aforementioned established association between low cognitive ability and vascular risk factors (e.g. smoking and physical inactivity) and cardiovascular diseases (e.g. stroke and coronary heart disease) suggests that CA could be strongly related to LOD. The association between early life CA and LOD has, however, not yet been explored as none of the previous studies have followed participants past the age of 55 years.

The overall objective of the study was to investigate the relation between young adult CA and MD in adult men. Specifically, we aimed to investigate 1) the relation between CA and EOD vs. LOD, 2) if CA is associated with the number of depressive episodes, and 3) whether the relation between CA and MD differs according to depression subtype (single depressive episode vs. recurrent depression) and severity of the depressive episode (mild, moderate, and severe, or, with or without psychotic features).

Based on proposed theories and previous findings we hypothesized that men with low CA have a higher risk of developing MD and have more depressive episodes than men with high CA. Moreover, we expected that the relation between CA and MD will be stronger for LOD compared to EOD because of the relation between CA and both vascular risk factors and chronic diseases associated with the risk of MD and LOD in particular. Finally, we hypothesized that the relation between CA and MD will be stronger for recurrent depression and for the most severe depressive episodes.

2 Methods
2.1 Study population
The study was based on data from the Danish Conscription Database (DCD) – a cohort established by digitizing information collected at the Danish conscription board examinations. All Danish men are required by law to appear before the conscription board between the age of 18 and 26, and the DCD is a cohort of 728,159 men born predominantly from 1939 through 1959 and examined from 1957 through 1984. The unique personal identification numbers of the DCD men were traced in the
Danish Civil Registration System, a register of all residents in Denmark from April 1968 and onwards (Pedersen, 2011). A very small proportion (0.2%, n=1617) was excluded because the personal identification numbers were registered as inactive making the registry information unreliable. Furthermore, 7.2% (n=52,139) were excluded because they did not have any examination data. The missing examination data were a result of some men being exempted from the conscription board examination due to medical conditions (e.g. epilepsy, type 1 diabetes, and intellectual disability) that would have rendered them unfit for military service. The DCD has been described in more detail in Christensen et al. 2015 (Christensen et al., 2015).

2.2 Exposure: Cognitive ability (CA)
CA was assessed at the conscription board examination by an intelligence test called the Børge Prien Prøve (BPP) (Teasdale, 2009). The BPP is a timed paper and pencil test comprising four subtests: letter matrices (19 items), verbal analogies (24 items), number series (17 items), and geometric figures (18 items). The number of correct answers has been summed into a total score with a range of 0-78. This total BPP-score has been shown to correlate substantially (r=.82) with the full-scale Wechsler Adult Intelligence Scale IQ-score (Mortensen et al., 1989), the most widely used clinical test of intelligence. Information on the individual subtest scores was not available and information on the full BPP-score was missing for 5684 (0.8%) of the DCD men.

2.3 Outcome: Major depression (MD)
Information on MD was retrieved from three Danish nationwide registers: the Danish Psychiatric Central Research Register (DPCRR) (Mors et al., 2011), the Danish National Patient Register (DNPR) (Lynge et al., 2011), and the Danish Register of Causes of Death (DRCD) (Helweg-Larsen, 2011). Information on date of admission and main and contributory diagnoses have been registered for all admissions to a psychiatric or somatic ward in the DPCRR and the DNPR since 1969 and 1977, respectively. From January 1st 1995 the DPCRR became an integrated part of the DNPR and information on outpatient treatment in psychiatric ambulatories and community psychiatry centers, as well as emergency room contacts was included. The DRCD contains information on the main and contributory causes of all deaths occurring from 1970 and onwards. In all three registers diagnoses have been registered according to the 8th Revision of the International Classification of Diseases (ICD-8) system from 1969 through 1993 and according to ICD-10 from 1994 and onwards. The main outcome of interest in the present study was defined as first hospital discharge
or death with a main or contributory diagnosis of MD (ICD8: 296.0, 296.2, 298.0, 300.4 and ICD10: F32, F33) from 1969 through 2015.

In accordance with previous studies we defined LOD as MD diagnosis at first hospital discharge or death after the age of 60 years (Driscoll et al., 2005; Variend and Gopal, 2008). We further investigated the relation between CA and number of depressive episodes. To delimitate individual depressive episodes from multiple hospitalizations due to relapse the number of depressive episodes was defined as the number of registrations with an MD diagnosis in the three aforementioned registers that were at least 6 months apart. Finally, with the introduction of ICD-10 codes the diagnostic classification of MD has become more detailed, which allows for more detailed analyses of the depression subtype and severity. Depression subtype: Based on the medical history the physician registers whether the patient is suffering from a single depressive episode (ICD10: F32) or a recurrent depression (ICD10: F33), that is if the patient has had a prior diagnosis of depression regardless of whether the diagnosis was made in hospital, general practice or by a private practicing psychiatrist. Severity: The depressive episodes are also classified into mild (ICD10: F32.0, F33.0), moderate (ICD10: F32.1, F33.1), and severe depression (ICD10: F32.2, F32.3, F33.2, F33.3) and information on whether the episode has psychotic features (ICD10: F32.3, F33.3) is also registered.

2.4 Covariable: Education
Education is associated with MD (Schaakxs et al., 2017) and is correlated with CA (Neisser et al., 1996) and may thus confound or moderate the relation between CA and MD. Information on education was based on self-reported current level of education at the time of the conscription board examination. Education was coded into three categories comprising low education (7-9th grade), a medium level of education (vocational training or 10-11th grade), and a high educational level (12th grade or more). In addition to the observations with missing information on the BPP-score, information on educational attainment was missing for 1180 (0.2%) of the DCD men.

2.5 Statistical analysis
The associations between young adult CA and MD, depression subtype and severity were analyzed using Cox regression with age as the underlying time scale. The study population covers 21 birth cohorts (from 1939 to 1959) and it has previously been shown that the mean BPP-score increases with increasing birth year (Christensen et al., 2015). The models were consequently stratified by birth year to control for the potential effect of calendar time.
CA and MD: For the main analysis of CA and MD, person-years of follow-up were accumulated from either 1st of January 1969, when registration of psychiatric admissions began, or from the date of conscription board examination for those examined after 1969. Follow-up ended at the date of 1) first admission for MD, 2) emigration, disappearance or death, or 3) the 31st of December 2015, whichever came first. A small proportion of men (n=723, 0.1%) were excluded from the analyses because they emigrated, disappeared, or died before 1st of January 1969 (n=656, 0.1%), 2) or because they were registered with a diagnosis of MD before study entry (n=67, 0.01%).

CA and number of depressive episodes: The association between young adult CA and number of depressive episodes was analyzed using linear regression among those men who had at least one MD diagnosis and who were followed for at least 6 months after the initial episode. The distribution of depressive episodes was skewed and was thus log-transformed to meet the assumption of the normally distributed outcome. Because the DCD covers 21 birth cohorts the length of follow-up varied considerably. Consequently, the follow-up time was included as an independent variable in the linear regression model to adjust for this difference in follow-up time.

CA and depression subtypes and severity: As described depression subtypes and severity were classified according to ICD-10, hence, person-years of follow-up were accumulated from 1st of January 1994, when ICD-10 was implemented in Denmark. Given the redefined study entry a proportion (n=43,309, 5.9%) of men were excluded from the analyses because they emigrated, disappeared, or died before 1st of January 1994 (n= 36475, 5.0%) or were registered with a diagnosis of MD before study entry (n= 6834, 0.9%).

The proportional hazards assumption was examined graphically by plotting Schoenfeld residuals and inspecting log-log survival curves for the association between MD and CA (grouped in quintiles). The distance between the curves was relatively constant up until age 60 from which it diminished. Consequently, all analyses were split at age 60, which is also the age chosen as the cut-off for LOD, and the proportional hazards assumption was no longer violated. For the analyses of depression subtypes and severity only associations between CA and MD from study entry until age 60 were reported due to a low number of MD cases after age 60. The assumption of linearity was tested by including a quadratic and a log-transformed term of the BPP-score (cognitive ability) in the model. Neither of the added terms were statistically significant and they were therefore excluded. Interactions between CA and birth cohort or education were examined by comparing models with and without an interaction term using likelihood ratio tests. There was no indication of significant multiplicative interaction. Given that some subjects might have died before they could
have been admitted with MD it is important to take competing risks into account (Andersen et al., 2012). This was done using Fine Gray competing risk regression by the stcrreg command in STATA. In the present study, the estimates from the two models were practically identical for all outcomes (see supplementary Table 1 for the subdistribution hazard ratios). This suggested that the estimated associations from the Cox regression model were not substantially affected by the presence of competing risks. Consequently, we report the estimates from the Cox regression model, because they are more easily interpreted.

As a sensitivity analysis we excluded men who were diagnosed with MD within the first year and first five years of their conscript board examination to limit the possibility of their performance on the intelligence test being affected by undiagnosed MD.

When applicable a Wald test was used to compare point estimates. All analyses were carried out in STATA version 14.

3 Results
The study population consisted of 666,804 men of which 25,841 (3.9% (ICD8: 4468; ICD10: 21,385)) were registered with a hospital diagnosis of MD during the follow-up period (mean time at risk=40.8 years). Table 1 presents the relation between covariables and CA (BPP-score) and MD, respectively. The mean BPP-score increased with increasing birth year and it was almost two standard deviations (SDs) higher in men with high compared to low education. The proportion of MD cases was equally distributed across birth years, but higher in those with low compared to high education (4.6% vs. 3.4%).

Cognitive ability and MD: As presented in table 2 a total of 19,015 (2.9%) of the 666,804 men in the study population had a first hospital diagnosis of MD from young adulthood until age 60 (median follow-up: 37.5 years; range: 0.0-46.0 years). In the 467,907 men who survived until age 60 and had no prior MD diagnosis 6838 (1.5%) developed MD at a later age (median follow-up: 7.6 years; range: 0.0-24.5 years). In analyses adjusted for age and year of birth (model 1) an inverse association was found between young adult CA and MD and the association was stronger for early-onset (HR\textsubscript{per1SD decrease}=1.23, 95%CI: 1.21,1.24) compared to late-onset (HR\textsubscript{per1SD decrease}=1.14, 95%CI: 1.11,1.16) MD (p<.001). Further adjusting for educational level at time of conscription (model 2) did not change the results.

CA and number of depressive episodes: The number of depressive episodes ranged between 1 and 13 in the population of 25,804 men who were registered with at least one episode of MD and who were followed for at least six months after the initial episode. However, only a small
proportion (8.8%) of the population had 3 or more episodes, and CA was not associated with the number of depressive episodes in the crude analysis ($\beta_{\text{per1SDdecrease}}=-1.47 \times 10^{-4}; 95\%\text{CI}: -2.90 \times 10^{-4}, -5.84 \times 10^{-4}$) or when adjusting for the difference in follow-up time between individuals ($\beta_{\text{per1SDdecrease}}=-1.77 \times 10^{-3}; 95\%\text{CI}: -1.02 \times 10^{-3}, 3.48 \times 10^{-3}$).

The associations between CA and MD subtypes and severity were analyzed in the 623,480 men who were alive on January 1st 1995 (the date of the introduction of ICD10 codes) and had no prior diagnosis of MD. Inverse associations between CA and MD were found for both single depressive episode ($HR_{\text{per1SDdecrease}}=1.21; 95\%\text{CI}: 1.19, 1.23$) and recurrent depression ($HR_{\text{per1SDdecrease}}=1.13; 95\%\text{CI}: 1.09, 1.16$) (model 1), but the association was strongest for single depressive episodes ($p<0.001$). Adjusting for educational level at time of conscription did not affect the estimates (model 2).

Inverse associations were found between CA and mild, moderate, and severe MD (model 1). The estimates were of a similar magnitude ($HR_{\text{per1SDdecrease}}=1.17-1.21$) and the confidence intervals were overlapping for the three categories of severity. However, using the presence of psychotic features as an indicator of severity revealed a somewhat stronger association between CA and MD with ($HR_{\text{per1SDdecrease}}=1.27; 95\%\text{CI}: 1.17, 1.38$) compared to without ($HR_{\text{per1SDdecrease}}=1.18; 95\%\text{CI}: 1.16, 1.20$) psychotic features, although the difference between the estimates was not significant ($p=0.11$) (model 1). Adjusting for educational level at time of conscription did not affect the estimates (model 2).

We found similar results in the analyses excluding MD cases diagnosed within a year and within five years of the conscription board examination (data not shown).

4 Discussion

4.1 Summary of findings

In this study of 666,804 men of which 3.9% were registered with a first hospital diagnosis of MD, lower CA in young adulthood was associated with an increased risk of MD later in adult life. The association was strongest for EOD (<60 years) compared to LOD (≥60 years). Moreover, for EOD the association between CA and MD was strongest for single depressive episodes compared to recurrent depression. Young adult CA was not associated with the number of depressive episodes and there was no difference in the strength of associations in relation to disease severity.

4.2 Comparison with previous findings
In line with our hypothesis and with most previous studies we found an inverse association between young adult CA and MD in adulthood. Previous studies have reported an inverse association for MD assessed by hospital diagnosis (Gale et al., 2010; Sorensen et al., 2012; Urfer-Parnas et al., 2010; Zammit et al., 2004) and structured diagnostic interviews (Gale et al., 2008; Koenen et al., 2009), whereas the findings from two studies using self-reported measures of depression or depressive symptoms were conflicting (Hatch et al., 2007; Wraw et al., 2016).

This is the first study of early life CA and adult MD with a follow-up period extending beyond the age of 60. Contrary to our hypothesis the association between young adult CA was significantly stronger for EOD compared to LOD. This may suggest that the influence of CA on early life stressors and the ability to cope with these stressors is stronger than the association between CA and vascular risk factors (e.g. smoking and physical activity) and chronic diseases (e.g. type 2 diabetes, coronary heart disease, and stroke) that have been related to the risk of developing LOD potentially due to pathological changes in the brain. It is also possible that CA and EOD share genetic factors given that both CA and EOD has been shown to be moderately to highly heritable (Goltser-Dubner et al., 2010; Hjelmborg et al., 2006). It should, however, be observed that the study population is relatively young with cohort members being between 56 and 76 years old at the end of follow-up which has limited the follow-up period after age 60 (median follow-up: 7.6 years; range: 0.0-24.5 years). Investigating the relation between CA and EOD and LOD, respectively, in cohorts with a longer follow-up into old age will help clarify if men with low CA are particularly vulnerable to developing EOD compared to LOD.

Contrary to our expectations CA was not associated with the number of depressive episodes defined as the number of registrations with an MD diagnosis that were at least 6 months apart in the present study. Two studies have investigated the association between CA and number of hospital admissions or admission rates in male populations. In line with the present study a study by Zammit et al (Zammit et al., 2004) found no relation between young adult CA and number of hospital admissions for severe depression. In contrast, the study by Gale et al (Gale et al., 2010) found low CA to be associated with high hospital admission rates for mood disorders. However, these results might not be comparable because the men in the present study could have more than one admission per depressive episode. The results from the present study suggest that CA is related to being hospitalized with MD, but that after the first admission for MD those with high and low scores have similar risks of experiencing another depressive episode requiring inpatient care.
Against our hypothesis, the relation was strongest for single depressive episodes compared to recurrent depression. However, together with the finding that CA was not related to number of depressive episodes this suggests that CA is primarily related to risk of having a first hospitalization for MD and that the influence of CA on later admission with MD is more limited.

None of the other studies using hospital diagnosis of MD has investigated the relation between CA and severity of MD using the ICD-10 codes for mild, moderate, and severe MD. Contrary to what was expected there was no difference in associations for the three groups in the present study. Although the difference was not significant the association between CA and MD with psychotic features seemed stronger than for MD without psychotic features. However, this may reflect a general association between low CA and a disposition to develop psychotic features rather than an association between CA and severity of MD.

In the present study adjusting for education had no effect on the estimated associations. Whether it is meaningful to adjust for education is debatable, because CA will be a factor that influences educational success and adjusting for education will thus limit the variation in CA in the analysis.

4.3 Strengths
A major strength of the present study is the large cohort and long follow-up, which has resulted in a large number of cases with a limited loss to follow-up (emigration 2.5%). The population based nature of the cohort and the fact that all men are required by law to appear before the conscription board, limit the possibility of selection bias. Further, the combination of free and universal access to health care and nationwide registration of all hospital admissions ensures that information on the outcome was based on a clinical diagnosis, and that the information was collected prospectively in a standardized manner without risk of recall bias.

4.4 Limitations
MD was defined on the basis of hospital admissions and thus the present study only includes severe MD cases. In another study, in which MD was defined on the basis of hospital admission with MD or purchase of at least two antidepressant prescriptions, the authors found that only 12.2% of MD cases were based on hospital diagnoses (Jorgensen et al., 2016) suggesting that MD is underestimated in the present study. On the other hand, approximately 50% of all antidepressants are prescribed for other purposes than depression, and using prescription fillings could thus lead to misclassification (Wong et al., 2016). In addition the severity of the disease is not the only factor affecting the likelihood of being admitted to hospital since resources such as high socioeconomic
position (SEP) and strong social network will also affect the likelihood of being admitted to a psychiatric department. Our results could thus partly reflect that people with low CA are more likely than people with high CA to be referred to inpatient care, regardless of the severity of their condition. Thus, it is likely that the association between CA and MD would be different had less severe cases not needing hospitalization been included. However, investigating the mediating effects of SEP and social network, as well as other mediating factors such as vascular risk factors, was beyond the scope of this paper and thus remains an important issue for future studies.

Even though we excluded men who were diagnosed with MD before conscription it is possible that undiagnosed MD at conscription could have affected the result of the CA test. However, we found similar results when excluding those receiving a hospital diagnosis of MD within the first year and first five years after their conscription board examination. On the other hand, impaired cognition is a part of the diagnostic criteria for MD, and MD might be overestimated in those with low CA if clinicians do not take premorbid CA into account in their assessment.

Finally, the lack of data on women is a limitation of the present study and whether the results can be generalized to women is uncertain. Depression is often found to be more prevalent among women, but previous findings with regard to sex differences of the association between early life CA and MD are conflicting. A study by Wraw et al. found similar associations for men and women (Wraw et al., 2016), whereas a study by Hatch et al. only found an association for women, but not for men (Hatch et al., 2007).

4.5 Conclusion
Lower premorbid CA in young adulthood seems to be a risk factor for MD in men especially for single depressive episodes with early-onset whereas the influence of premorbid CA on re-occurrence is less strong. Premorbid CA should therefore be part of the depression risk assessment in clinical practice.

Conflict of Interest
The authors declare that they have no conflict of interest.

Author statement

Contributors
A) GT Christensen, B) M P Rozing C) E L Mortensen D) K Christensen E) M Osler
Authors A and E were involved in the design of the study. 
Author A, C, D, and E was involved in the acquisition of data. 
Author A performed the statistical analyses. 
All authors have contributed to the interpretation of the results. 
Author A wrote the first draft of the manuscript. 
All authors have participated in the critical revision of the manuscript for important intellectual content and have contributed to subsequent drafts. 
All authors have approved the submitted manuscript.

Role of the Funding Source

This work was supported by the Danish Medical Research Council [grant numbers 09-063599 and 09-069151] and the Velux Foundation [grant number 31205]. The funding sources had no involvement in the conduct of the research or in the preparation of the article.

Acknowledgements

No additional acknowledgements are applicable.

References


Table 1: Covariables in relation to cognitive ability (BPP-score) measured at conscription (age 19) and major depression followed from 1977 through 2015 for 666,804 men.

<table>
<thead>
<tr>
<th>Study population</th>
<th>Cognitive ability (BPP-score)</th>
<th>Major depression</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number, n (%)</td>
<td>Mean (SD)</td>
</tr>
<tr>
<td><strong>Birth year, N(%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1939-44</td>
<td>176,688 (26.5)</td>
<td>35.6 (12.7)</td>
</tr>
<tr>
<td>1945-49</td>
<td>186,109 (27.9)</td>
<td>37.7 (12.0)</td>
</tr>
<tr>
<td>1950-54</td>
<td>162,593 (24.4)</td>
<td>38.6 (11.6)</td>
</tr>
<tr>
<td>1955-59</td>
<td>141,414 (21.2)</td>
<td>39.8 (11.1)</td>
</tr>
<tr>
<td><strong>Education, N(%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>171,620 (25.7)</td>
<td>27.9 (9.9)</td>
</tr>
<tr>
<td>Medium</td>
<td>381,187 (57.2)</td>
<td>38.3 (9.7)</td>
</tr>
<tr>
<td>High</td>
<td>113,997 (17.1)</td>
<td>51.2 (7.4)</td>
</tr>
</tbody>
</table>

Abbreviations: BPP-score: Børge Prien Prøve score (intelligence test score)
Table 2. Age-adjusted hazard ratios (HRs) for the association between intelligence test score (Børge Prien Prøve (BPP)-score) measured at conscription and major depression in relation to age at onset, subtype, and severity.

<table>
<thead>
<tr>
<th>Age at onset</th>
<th>n cases</th>
<th>Model 1 HR*</th>
<th>95% CI</th>
<th>Model 2 HR*</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;60 years, n=666,804</td>
<td>19,004</td>
<td>1.23</td>
<td>1.21,1.24</td>
<td>1.21</td>
<td>1.18,1.23</td>
</tr>
<tr>
<td>&gt;=60 years, n=467,907</td>
<td>6837</td>
<td>1.14</td>
<td>1.11,1.16</td>
<td>1.17</td>
<td>1.13,1.20</td>
</tr>
</tbody>
</table>

Study population**, n=623,480 men

<table>
<thead>
<tr>
<th>Depression subtypes</th>
<th>n cases</th>
<th>Model 1 HR*</th>
<th>95% CI</th>
<th>Model 2 HR*</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single depressive episode</td>
<td>10,689</td>
<td>1.21</td>
<td>1.19,1.23</td>
<td>1.19</td>
<td>1.16,1.22</td>
</tr>
<tr>
<td>Recurrent depression</td>
<td>3823</td>
<td>1.13</td>
<td>1.09,1.16</td>
<td>1.14</td>
<td>1.09,1.19</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Depression severity</th>
<th>n cases</th>
<th>Model 1 HR*</th>
<th>95% CI</th>
<th>Model 2 HR*</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>925</td>
<td>1.21</td>
<td>1.14,1.30</td>
<td>1.22</td>
<td>1.12,1.32</td>
</tr>
<tr>
<td>Moderate</td>
<td>2785</td>
<td>1.18</td>
<td>1.14,1.23</td>
<td>1.18</td>
<td>1.13,1.24</td>
</tr>
<tr>
<td>Severe</td>
<td>5627</td>
<td>1.17</td>
<td>1.14,1.20</td>
<td>1.17</td>
<td>1.13,1.21</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Depression with psychotic features</th>
<th>n cases</th>
<th>Model 1 HR*</th>
<th>95% CI</th>
<th>Model 2 HR*</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>13,961</td>
<td>1.18</td>
<td>1.16,1.20</td>
<td>1.17</td>
<td>1.14,1.19</td>
</tr>
<tr>
<td>Yes</td>
<td>551</td>
<td>1.27</td>
<td>1.17,1.38</td>
<td>1.34</td>
<td>1.20,1.49</td>
</tr>
</tbody>
</table>

Abbreviations: CI=Confidence Interval, HR=Hazard ratio

*The results are expressed as the hazards ratio per 1 standard deviation decrease in intelligence test score (BPP-score)

**Restricted to men who were alive on January 1st 1994 (the date of the introduction of ICD-10 codes) and had no prior diagnosis of depression.

Model 1: Stratified by birth year
Model 2: Stratified by birth year and adjusted for educational level at time of conscription.