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Prevalence of major depressive disorder in 51,658 otherwise healthy adult Danes: Sex differences in symptomatology and prediction of future anti-depressive medication

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ABSTRACT

Major Depressive Disorder (MDD) is a heterogeneous disease, which displays sex differences in symptomatology. This study aimed to assess point prevalence of MDD in undiagnosed, healthy adults as well as sex differences in symptomatology and clarify if specific symptoms increased the later need for anti-depressive medication. The study included 51,658 blood donors. Depressive symptoms were assessed according to ICD-10 using the Major Depression Inventory. Demographics, previous MDD, anti-depressive medication were collected from questionnaires and population registers. Descriptive, Logistic and Cox regression analyses were conducted.

In total, 1.15% participants met the criteria for MDD. Women were significantly more likely to experience "increased appetite" and less likely to experience "a feeling of life not worth living", compared to men. MDD significantly associated with an increased hazard of later receiving a prescription for anti-depressive medication. The risk increased proportionally with increasing MDD severity. The two symptoms, "feeling that life is not worth living" and "trouble sleeping" were the strongest individual predictive symptoms of future anti-depressive medication in women and men, respectively.

The results confirm findings in MDD patient groups. The diagnostic and prognostic value should be investigated further to address their potential as part of the clinical assessment.

1. Introduction

Major Depressive Disorder (MDD) is a common psychiatric disorder, twice as common in women as in men (Kuehner, 2017), with a total prevalence in Denmark of just below 3% (Ellervik et al., 2014). The global prevalence estimate of people in need of treatment due to

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depression has increased with nearly 20% between 2005 and 2015 (World Health Organization, 2017) resulting in an increase in the related socioeconomic burden of great magnitude (Greenberg et al., 2015; Xu et al., 2016). Detection of MDD in early stages increases the probability of a positive treatment outcome significantly (Bukh et al., 2013; Halfin, 2007).

Evidence of the heterogeneity of MDD has emerged, suggesting numerous distinct subtypes (Harald, Gordon, 2012) not sufficiently described in the current diagnostic constructs. These includes symptom-based subtypes e.g. atypical depression which has been shown to be more frequent in women and present with neurovegetative symptoms including increased appetite and hypersomnia (Blanco et al., 2012; Lamers et al., 2013; Marcus et al., 2008). In addition, research suggests distinct biomarker differences among the different subtypes. Melancholic depression, characterized by loss of pleasure and lack of mood reactivity, has been found to associate with Hypothalamic-Pituitary-Adrenal axis hyperactivity (Esposito, Buoli, 2020), whereas atypical depression associates with immune and metabolic dysregulation (Lamers et al., 2020).

On a broader scale, a recent study assessed potential clinical and biochemical differences among MDD patients diagnosed according to DSM-5 and not stratified by subtype (Ceresa et al., 2022). Their findings suggest that women are more prone to metabolic dysregulation indicated by higher cholesterol and lower uric acid levels.

However, while the combined literature suggests a need for more a more personalized approach to MDD diagnostics, identification of early symptoms in (yet) *undiagnosed* individuals, pose a challenge. To assess this, large-scale prospective studies of individuals who are undiagnosed and otherwise healthy at baseline are needed. The Danish Blood Donor Study (DBDS) is a nationwide cohort of blood donors that enables such a study. The cohort was initiated in 2009 as a healthy prospective cohort study, which could be used to identify early disease parameters, both clinically and biochemically (Didriksen et al., 2018; Hansen et al., 2019; Pedersen et al., 2012). Combined with access to public registries and the national prescription database, the DBDS makes it possible to follow the participants' use of medication from enrollment, and until they emigrate from Denmark or their death.

The present study includes 51,658 blood donors, with no depressive disorder at baseline. The aim was to investigate the point prevalence of ICD-10 MDD in DBDS participants upon enrollment into the cohort and to elucidate potential sex-specific symptomatology. Furthermore, to reveal if specific early symptoms were associated with increased risk of later anti-depressive medication.

2. Methods

2.1. Study design and participants

The study is based on DBDS. Upon enrollment, participants answer an elaborate health questionnaire, including items on depressive symptoms and they give permission for individual-level linkage to data from national registers (Burgdorf et al., 2017; Pedersen et al., 2012). To be eligible for blood donation the donors are required to be generally good health and not undergoing chronic medical treatment for example anti-depressive medication. Their general health is assessed in a face-to-face interview with a health care professional or donor care assistant. Data was retrieved between May 19, 2015 and December 31, 2021.

2.2. Depressive symptoms and investigated characteristics

The Major Depression Inventory (MDI) has previously been validated in the Danish population (Bech et al., 2001, 2015) and between 2015 and 2018 it was included in the DBDS inclusion-questionnaire. Participants were also asked if they have ever been diagnosed with depressive disorder by a medical doctor. If participants answered yes to this question, they were asked whether they received medical or other treatment.

In this study, MDD was defined using MDI according to the ICD-10 classification as the presence of at least two core symptoms and two accompanying symptoms. Presence of at least two core- and two accompanying symptoms indicate mild depression, at least two core and four accompanying symptoms indicate moderate depression, and at least three core- and five accompanying symptoms indicate severe depression.

The participants were linked with data from the Danish National Prescription Register and from the Occupation register. This was done by using pseudomized versions of the unique civil Danish registration numbers (Pedersen, 2011). Information on filled prescriptions for anti-depressive medication (Anatomical Therapeutic Chemical (ATC) classification codes: N06A) was collected in the years between January 1995 and December 31, 2021. Moreover, information on the participants' highest achieved educational level was retrieved. Data on weight, height, smoking status, and alcohol consumption was self-reported. Data on sex and age were collected from national population registers. Data on donation history was available from all national blood bank registers.

2.3. Mental health-related quality of life

Mental health-related quality of life (MCS) in the current cohort was assessed by the 12-item short form healthy survey (SF-12) and calculated by applying the method recommended by Quality Metric Inc (Steenstrup et al., 2013).

2.4. Statistics

The study population was described using descriptive statistics. Age and body mass index (BMI) were described by means and standard deviations (SD), while dichotomous and categorical variables were described in percentages. Differences between groups were investigated using t-tests for normally distributed data and Mann-Whitney U-tests for non-normally distributed data. Chi^2-tests were used to assess differences in distribution of dichotomous variables. Normal distribution of data was investigated by producing quantile-quantile plots and to obtain normal distribution, age was log-transformed. Sex-stratified multivariable Cox regression models were used to assess the association between depressive symptoms and risk of subsequently being prescribed anti-depressive medication. The analyses were adjusted for age, obesity ($BMI \geq 30$ (Bremner et al., 2020)), smoking status (Fluharty et al., 2017; Wang et al., 2018), educational level (Bjelland et al., 2008; Han et al., 2019; Llorente et al., 2018), alcohol consumption (Keyes et al., 2019), and use of anti-depressive medication prior to study enrollment. A P-value<0.05 was considered statistically significant. Statistical analyses were conducted on Statistics Denmark servers on anonymized data using STATA/SE 15.0, StataCorp, College Station, TX.

3. Results

3.1. MDD results and the association with future prescription of anti-depressive medication

In total, 51,658 participants (25,109 women and 26,549 men) were included in the analyses (Fig. 1). Characteristics of the study population can be found in Table 1. In total, 596 (1.15%) participants (63.8% women), classified with an ICD-10 depression at baseline and of these, 158 (26.6%) (n, women=124) reported a previous MDD diagnosis (Table 2).

When examining the mean scores of the individual MDI items, the following symptoms displayed sex differences: *lacking energy, trouble concentrating, increased appetite* and *life not worth living* (Table 3). The first three most common in women whereas the latter was most common in men. Overall, the two core symptoms *lack of interest* and *lacking energy*

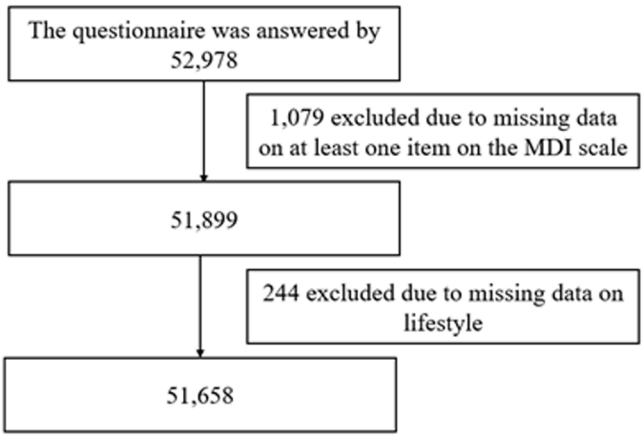

Fig. 1. Flowchart of participant inclusion in the analysis. All participants answering the questionnaire was eligible for inclusion. Exclusion criteria included missing data in the MDI questions, no information on smoking, bmi or alcohol consumption.

Table 1
Baseline characteristics of the study population.

Characteristic	Current ICD-10 depression	No current ICD-10 depression	P value[‡]
Participants	596	51,062	
Sex (women), n (%)	380 (63.8)	24,729 (48.4)	<0.001
Age (years), mean (SD)	32.5 (11.3)	40.3 (13.0)	<0.001
Smoking (%)	21.8	13.1	<0.001
Self-reported previous depression diagnosis (%)	26.6	8.1	<0.001
Previous use of anti-depressive medicine (%)	18.9	7.95	<0.001
Body mass index, mean (SD)	26.3 (4.8)	25.7 (4.2)	<0.001
Alcohol drinking (%)			<0.001
Almost never	25.2	14.4	–
A few times a month	54.4	51.6	–
A few times a week	16.8	29.7	–
Every day	3.7	4.3	–
Education (%)			<0.001
Elementary/middle school	13.2	7.63	–
High school/vocational course	49.3	45.5	–
Short length higher education	6.51	8.26	–
Medium length higher education	20.4	24.3	–
Long length higher education	10.6	14.3	–

[‡] Participants with ICD-10 depression (≥2 core symptoms and ≥2 accompanying symptoms) compared to controls.

had the highest mean scores among both women and men.

3.2.1. Investigating risk of later treatment with anti-depressive medication

During follow-up of the entire cohort, 1874 (3.63%) participants (58.7% women) received a prescription of anti-depressive medication. In total, 97 (16.3%) (71 women) of the participants who classified with an MDD at baseline filled a prescription for anti-depressive medication during follow-up (median number of days after inclusion = 897, inter quartile range (IQR): 211–1356). Of all the 1874 participants, 628 (33.6%) reported having a previous depression diagnosis. For the Cox regression analysis, the date of entering was set as the date of enrollment in the DBDS and thus answering the MDI. The earliest date of entry was therefore May 19th, 2015, while the latest date was June 1, 2018. Date of censoring was set as prescription date, date of death, or December 31, 2021, whichever came first. Data on deaths was only available until December 31, 2018. This means that if any participants died between January 1, 2019 and December 31, 2021 they have been misclassified as controls in the Cox regression models. However, since the mean age of the study population is 40 years, they are generally healthy upon inclusion, and the recorded death rate prior to 2019 is low, it is unlikely that this will have biased the results. If this has had any effect, it would have been a decrease in effect estimates. Mean follow-up time was 5.1 years (a total of 264,922 person-years). Participants classifying with ICD-10 depression according to MDI at baseline had an increased hazard ratio (HR) for subsequently being prescribed anti-depressive medication (women, HR = 4.90 (95% CI: 3.85–6.23), $P<0.001$; men, HR = 4.44 (95% CI: 3.00–6.56), $P<0.001$). The hazard was observed to be dependent on symptom severity (Table 4).

3.2. Symptoms predicting later medical treatment

When investigating the individual symptoms and risk of later being prescribed anti-depressive medication, some notable findings occurred:

First, the cox regression analysis was only corrected for known confounders (Table 5, Model A). Thereby assessing the predictive value of the individual symptoms when other depressive symptoms are also present. In the total cohort, presence of each individual symptom, associated with increased hazard of later anti-depressive medication. However, when only including individuals classifying with MDD at baseline, it was observed that in women, symptoms of *sadness* (HR = 1.86; 95% CI: 1.12–3.07, $P = 0.016$), *guilt* (HR = 2.37; 95% CI: 1.24–4.53, $P = 0.009$), and *life not worth living* (HR = 2.55; 95% CI: 1.52–4.29, $P = <0.001$), each significantly increased the risk of anti-depressive medication. This suggests that if one or more of these symptoms are part of a female patient's symptomatology, then there is an increased risk of progression with ensuing need for medical treatment.

To assess the predictive value of each individual symptom without the presence of other symptoms, the analysis was repeated with correcting for the remaining symptoms (Table 5, Model B). Here it was found that different symptoms associated with anti-depressive medication both in women and men, but also dependent on MDI-score at baseline. In participants with baseline depression, problems *concentrating* (men, HR = 2.62; 95% CI: 1.03–6.62, $P = 0.044$) and *life not worth living* (women, HR = 1.62; 95% CI: 1.07–3.43, $P = 0.028$) significantly increased the risk of anti-depressive medication.

3.3. MCS and iron deficiency

A negative correlation was observed between the MDI and the MCS score (linear regression coefficient=−0.53. $p<0.001$). Furthermore, analysis also showed a negative correlation between MCS and risk of later being prescribed anti-depressive medication. The risk decreased by 6% for each 1-point increase in MCS.

As iron deficiency is a known side effect to blood donation with symptomatology that may mimic depression, this was also included in the analyses. Previous studies have described that donation history for the past 3 years, is the strongest predictor for iron deficiency (Rigas et al., 2014). Consequently, follow-up analyses with this information was included as a covariate in all applied statistical models were conducted. The effect sizes were marginally attenuated, but the P-values did not change, suggesting that the depressive symptoms observed are independent of potential donation-related loss of iron.

4. Discussion

In this prospective cohort study of 51,658 otherwise healthy Danish blood donors, the point prevalence of MDD defined by MDI-score was 1.15% (0.81% among men and 1.52% among women).

Increased appetite and problems concentrating were significantly more common in women whereas men were more likely to experience a feeling of life not worth living. Together with sleep problems, life not

Table 2
ICD-10 Depression and previous anti-depressive medication among DBDS participants.

	All participants (N = 51,658)		Participants *without* a previous depressive diagnosis (N = 47,291)		Participants *with* a previous depression diagnosis (N = 4,274)	
	N	%	N	%	N	%
No current ICD-10 depression		98.9	46,854	99.1	4,116	96.3
(men/women)	51,062 (26,333/24,729)	(99.2/98.4)	(24,790/22,062)	(99.3/98.9)	(1,497/2,619)	(97.8/95.5)
Mild ICD-10 depression	217	0.42	166	0.35	51	1.19
(men/women)	(85/132)	(0.32/0.53)	(72/94)	(0.29/0.42)	(13/38)	(0.85/1.39)
Moderate ICD-10 depression	264	0.51	197	0.42	66	1.54
(men/women)	(93/171)	(0.35/0.68)	(80/117)	(0.32/0.52)	(12/54)	(0.78/1.97)
Severe ICD depression	115	0.22	74	0.16	41	0.96
(men/women)	(38/77)	(0.14/0.31)	(29/45)	(0.12/0.20)	(9/32)	(0.59/1.17)
Previous anti-depressive medication	–	–	–	–	2,109	49.3
(men/women)					(756/1,353)	(49.6/49.4)

Table 3
Mean score in participants with ICD-10 depression (N = 596).

Item	Symptom	ICD-10 depression Mean score, median (IQR†) Men (n = 216)	Women (n = 380)	P value‡
1§	Sadness	3.28, 3 (3;4)	3.29, 4 (2;4)	0.77
2§	Lack of interest	3.98, 4 (4;4)	3.92, 4 (4;4)	0.36
3§	Lacking energy	3.98, 4 (4;4)	4.16, 4 (4:4)	**<0.01**
4	Low self-esteem	3.17, 4 (3;4)	3.26, 4 (3;4)	0.20
5	Guilt	2.91, 3 (2;4)	3.08, 4 (2;4)	0.09
6	Life not worth living	1.34, 1 (0;2)	1.07, 1 (0;1)	0.03
7	Difficulties concentrating	1.97, 2 (1;3)	2.32, 3 (1;4)	**<0.01**
8a	Restless	2.42, 3 (1;4)	2.30, 2 (1;4)	0.41
8b	More quiet	2.88, 3 (2;4)	2.93, 3 (2,4)	0.66
9	Trouble sleeping	2.50, 3 (1;4)	2.51, 3 (1;4)	0.95
10a	Decreased appetite	1.46, 1 (0;3)	1.42, 1 (0;3)	0.85
10b	Increased appetite	1.08, 0 (0;2)	1.79, 1 (0;3)	**<0.001**

† IQR = Inter quartile range.
‡ P-values for statistically significant differences between sexes were calculated using Mann-Whitney U tests because data were skewed to the right and therefore not normally distributed.
§ Core symptoms.

worth living were the strongest, individual predictive symptoms of receiving a prescription for anti-depressive medication.

The prevalence observed in this study was substantially lower than previous findings in Danish population studies, which reported prevalence from 2.3% and 4.9% (Andersen et al., 2011; Ellervik et al., 2014; Grynderup et al., 2012; Olsen et al., 2004). This difference is likely the result of the healthy donor effect (Atsma, de Vegt, 2011). A term which describes the phenomenon of decreased morbidity rates and healthier lifestyle among blood donors compared to the general population. This is supported by previous studies reporting that blood donors to have a better self-perceived mental health and higher Mental Component Score than the background population(Didriksen et al., 2021; Rigas et al., 2019a) In addition, we found that MDI score correlated negatively with the mental component score on the SF-12.

The sex differences in symptomatology reported here are in accordance with the findings from a 2017 meta-analysis of 32 studies with 108,260 individuals (Cavanagh et al., 2017). There, women were found to report depressed mood, appetite, and sleep disturbances more often. Suicidal thoughts was instead found to be more frequent in men, but this was not statistically significant. However, the heterogeneity in the data and the methods used to assess MDD was a concern. A recent Swiss study that used the Hamilton Depression Rating Scale to assess 590 MDD patients, found that women more frequently experience anxiety symptoms and guilt (Vetter et al., 2021). We equally found guilt to be more frequent in women however, this was not statistically significant. Our findings thus supports efforts towards a sex stratified assessment of potential depression exemplified by the Male Depression Risk Scale (Rice et al., al.,2022)

To our knowledge, this is the first study to combine the assessment of depressive symptoms among a group of otherwise healthy individuals with an investigation of the prospective association between specific symptoms and later anti-depressive medication. To address the individual association between each symptom and later anti-depressive medication, a fully adjusted model was performed to remove the effects from other symptoms. Interestingly, when stratifying by MDD or no MDD at baseline, we observed that different symptoms associated with increased hazards for later anti-depressive medication in the two groups. It could be speculated that the observed associations are the early symptoms of a developing MDD. In individuals classifying with depression at baseline, a different symptomatology was observed when investigating the hazard for being prescribed anti-depressive medication. In contrast to the no MDD group only one symptom associated with increased hazard for each sex. In women this was the same as in the no MDD group but for men, only problems in concentration significantly associated with later anti-depressive medication. Given, that these individuals already classified with MDD at baseline, further studies should investigate if the presence of these specific symptoms can be used as part of a prognostic tool.

This study has several strengths and potentials for translation into

Table 4
MDI score and risk of subsequently being prescribed anti-depressive medication. Cox regression analysis. (Reference group = no depression).

	Men, N = 26,549 Model 1 HR (95% CI)	P value	Model 2 HR (95% CI)	P value	Women, N = 25,109 Model 1 HR (95% CI)	P value	Model 2 HR (95% CI)	P value
ICD-10 depression	4.44 (3.00–6.56)	<0.001	2.58 (1.69–3.92)	<0.001	4.90 (3.85–6.23)	<0.001	3.03 (2.37–3.88)	<0.001
Mild depression	4.27 (2.29–7.98)	<0.001	3.26 (1.68–6.32)	<0.001	4.36 (2.85–6.64)	<0.001	3.55 (2.32–5.44)	<0.001
Moderate depression	3.54 (1.84–6.83)	<0.001	3.30 (1.70–6.37)	<0.001	3.99 (2.73–5.85)	<0.001	3.22 (2.18–4.77)	<0.001
Severe depression	7.17 (3.41–15.1)	<0.001	4.96 (2.05–11.9)	<0.001	8.22 (5.39–12.5)	<0.001	6.68 (4.37–10.2)	<0.001

Model 1: Unadjusted.
Model 2: Adjusted for age, smoking status, body mass index, alcohol intake, and educational level and previous use of anti-depressive medicine.

Table 5
Risk of being prescribed anti-depressant medication after experiencing specific depressive symptoms. Cox regression analysis.

MDI depressive symptom[†]	MODEL A								MODEL B							
	The total cohort, $N = 51,658$				Participants with depressive disorder according to MDI, $N = 596$				The total cohort, $N = 51,658$				Participants with depressive disorder according to MDI, $N = 596$			
	Men, $N = 26,549$		Women, $N = 25,109$		Men, $N = 216$		Women, $N = 380$		Men, $N = 26,549$		Women, $N = 25,109$		Men, $N = 216$		Women, $N = 380$	
	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
MDI 1	3.73 (2.51–5.54)	<0.001	3.37 (2.57–4.41)	<0.001	1.33 (0.55–3.22)	0.526	**1.86 (1.12–3.07)**	**0.016**	1.14 (0.70–1.85)	0.591	1.25 (0.89–1.77)	0.202	0.77 (0.55–5.67)	0.337	1.44 (0.80–2.56)	0.224
MDI 2	2.25 (1.63–3.10)	<0.001	2.36 (1.85–3.01)	<0.001	1.46 (0.32–6.53)	0.624	0.86 (0.44–1.66)	0.648	0.86 (0.57–1.28)	0.456	0.89 (0.64–1.22)	0.461	1.85 (0.36–9.40)	0.458	1.19 (0.56–2.53)	0.649
MDI 3	2.95 (2.25–3.87)	<0.001	2.65 (2.19–3.21)	<0.001	1.34 (0.31–5.82)	0.698	0.75 (0.27–2.12)	0.593	1.40 (0.99–1.99)	0.060	1.26 (0.96–1.66)	0.099	1.74 (0.35–8.75)	0.502	0.90 (0.29–2.74)	0.849
MDI 4	3.13 (2.50–3.93)	<0.001	2.54 (2.15–2.99)	<0.001	1.58 (0.52–4.82)	0.422	1.83 (0.87–3.85)	0.110	**1.55 (1.10–2.19)**	**0.012**	1.26 (0.99–1.61)	0.062	1.74 (0.53–5.65)	0.359	1.06 (0.47–2.36)	0.888
MDI 5	3.17 (2.54–3.96)	<0.001	2.69 (2.28–3.19)	<0.001	0.68 (0.29–1.60)	0.376	**2.37 (1.24–4.53)**	**0.009**	**1.67 (1.21–2.30)**	**0.002**	**1.46 (1.14–1.85)**	**0.002**	0.48 (0.18–1.30)	0.151	1.92 (0.95–3.89)	0.069
MDI 6	2.89 (1.92–4.35)	<0.001	4.12 (3.01–5.65)	<0.001	1.47 (0.60–3.62)	0.398	**2.55 (1.52–4.29)**	**<0.001**	1.20 (0.76–1.90)	0.425	**1.61 (1.12–2.36)**	**0.011**	1.30 (0.50–3.39)	0.597	**1.92 (1.07–3.43)**	**0.028**
MDI 7	2.63 (1.97–3.49)	<0.001	2.29 (1.85–2.86)	<0.001	2.15 (0.94–4.95)	0.071	1.38 (0.85–2.25)	0.192	1.20 (0.84–1.70)	0.317	0.89 (0.67–1.17)	0.398	**2.61 (1.03–6.62)**	**0.044**	0.96 (0.56–1.66)	0.883
MDI 8a	2.40 (1.88–3.07)	<0.001	2.62 (2.15–3.19)	<0.001	0.76 (0.33–1.74)	0.517	1.78 (1.08–2.92)	0.023	1.15 (0.84–1.58)	0.382	**1.32 (1.02–1.71)**	**0.038**	0.50 (0.20–1.28)	0.148	1.47 (0.84–2.57)	0.178
MDI 8b	2.27 (1.76–2.92)	<0.001	2.51 (2.07–3.05)	<0.001	0.89 (0.37–2.15)	0.792	1.69 (0.97–2.94)	0.065	0.93 (0.67–1.29)	0.654	1.11 (0.86–1.44)	0.409	0.67 (0.26–1.72)	0.403	1.36 (0.75–2.44)	0.308
MDI 9	2.62 (2.14–3.21)	<0.001	2.26 (1.92–2.68)	<0.001	1.44 (0.60–3.47)	0.414	1.24 (0.77–2.00)	0.380	**1.85 (1.46–2.35)**	**<0.001**	**1.44 (1.18–1.77)**	**<0.001**	1.22 (0.49–3.05)	0.672	1.12 (0.68–1.86)	0.651
MDI 10a	2.32 (1.56–3.44)	<0.001	2.11 (1.58–2.82)	<0.001	1.57 (0.62–3.96)	0.342	1.05 (0.61–1.83)	0.854	0.83 (0.53–1.29)	0.397	0.94 (0.68–1.31)	0.724	1.44 (0.50–4.13)	0.495	0.84 (0.45–1.58)	0.594
MDI 10b	1.64 (1.21–2.21)	0.001	2.26 (1.85–2.76)	<0.001	1.56 (0.60–4.07)	0.362	1.15 80.69–1.91)	0.597	1.01 (0.73–1.40)	0.939	**1.41 (1.13–1.77)**	**0.002**	1.89 (0.66–5.30)	0.224	1.06 (0.62–1.84)	0.822

HR = Hazard ratio.

[†] A core symptom (items 1–3) is considered present if it is experienced "most of the time" or more often, while an accompanying symptom is considered present if experienced "a little bit more than half the time" or more often (items 4–10)

MODEL A: Analyses were adjusted for age, obesity, smoking status, alcohol intake and educational level, and previous use of anti-depressive medication

MODEL B: Analyses were adjusted for age, obesity, smoking status, alcohol intake and educational level, and previous use of anti-depressive medication *and* the remaining MDI symptoms.

depression diagnostics and estimation of prognosis. It was performed in a subgroup that is considered healthier that the general population, which can both be considered a strength of the study methodology as well as a limitation. The strength is given in the fact that the included individuals were unlikely to suffer from differential diagnosis at time of enrollment. This indicates that the observed depressive symptoms might be characterized as early diagnostic features. However, because blood donors have been found to be healthier than the background population on several parameters, it may be difficult to generalize the results.

Even so, the size of the cohort and the standardized use of the MDI, which has been validated in the general Danish population, are important strengths. In accordance with previous studies in MDD patients, we found that in healthy, undiagnosed individuals, increased appetite and lack of energy were more frequent in women than in men. The presence of these patterns even before a clinical diagnosis indicate that these symptoms may be important in future studies of early diagnostic features.

There are also several limitations to this study. First, as implied by the healthy donor effect, there is the matter of selection bias, as donors must comply with strict health criteria to be eligible for donation. In case of a donor reporting a current depression, they may therefore be deferred. Not because of blood quality but to protect the health of the donor. Second, other states of mind may mimic depression causing misclassification of the MDI score. These include grief, stress, and sadness due to recent stressful life events. Third, based on available data, somatic disease or previous manic episodes could not be excluded; however, no participants reported known diseases needing medical treatment at the time of the donor health interview and inclusion. Fourth, anti-depressive medication may be used to treat other diseases including anxiety, obsessive-compulsive disorder, eating disorders or pain. Because these indications for antidepressants are much more seldom than depression and because they are linked to depression, we do not believe these other indications influences the associations found. In addition, as we did not have access to the public register for psychiatric diagnoses, using ATC-codes was considered the most accurate follow-up possible. Furthermore, we were not able to stratify into MDD symptom-subtypes based on the MDI results. However, it could extremely interesting and relevant to investigate if the symptomatology patterns observed here differ among the different subtypes. Another important limitation when using prescriptions as a proxy for diagnosis is that prescriptions of anti-depressive medication also relate to the subjective assessment of the physicians and the patients' attitude towards medication. Finally, blood donation is associated with reduced iron stores (Rigas et al., 2019b), which have been speculated to affect occurrence of depression (Vulser et al., 2016).

5. Conclusion

In conclusion, MDD among blood donors is rare compared to the general Danish population. Small, significant sex differences in symptomatology were seen, as women were more likely to have increased appetite and lack of energy, comparable to previous studies in MDD patients. Blood donors with MDD had an increased risk of anti-depressive medication during follow-up, with specific symptoms increasing the hazard significantly. Our results may prove beneficial in early diagnostics and prognostics and should be investigated further, both on a broader level and among different depression subtypes.

CRediT authorship contribution statement

Christina Mikkelsen: Conceptualization, Formal analysis, Methodology, Writing – original draft, Validation, Writing – review & editing. **Margit A.H. Larsen:** Data curation, Funding acquisition, Project administration, Validation, Writing – review & editing. **Erik Sørensen:** Data curation, Funding acquisition, Project administration, Validation, Writing – review & editing. **Thomas Folkmann Hansen:** Data curation, Funding acquisition, Project administration, Validation, Writing – review & editing. **Susan Mikkelsen:** Data curation, Funding acquisition, Project administration, Validation, Writing – review & editing. **Christian Erikstrup:** Data curation, Funding acquisition, Project administration, Validation, Writing – review & editing. **Kaspar R. Nielsen:** Validation, Writing – review & editing. **Mie T. Bruun:** Data curation, Funding acquisition, Project administration, Validation, Writing – review & editing. **Henrik Hjalgrim:** Data curation, Funding acquisition, Project administration, Validation, Writing – review & editing. **Lars V. Kessing:** Methodology, Validation, Writing – review & editing. **Thomas Werge:** Methodology, Validation, Writing – review & editing. **Henrik Ullum:** Data curation, Funding acquisition, Project administration, Validation, Writing – review & editing. **Sisse R. Ostrowski:** Data curation, Funding acquisition, Project administration, Validation, Writing – review & editing. **Ole B. Pedersen:** Data curation, Funding acquisition, Project administration, Validation, Writing – review & editing. **Lise W. Thørner:** Data curation, Funding acquisition, Project administration, Validation, Writing – review & editing. **Maria Didriksen:** Conceptualization, Formal analysis, Methodology, Writing – original draft, Validation, Writing – review & editing.

Declaration of Competing Interest

LVK has during recent three years been a consultant for Lundbeck. The remaining authors declare no conflicts of interest

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References

Andersen, I., Thielen, K., Nygaard, E., Diderichsen, F., Bech, P., 2011. Increasing prevalence of depression from 2000 to 2006. Scand. J. Public Health. https://doi.org/10.1177/1403494811424611.

Atsma, F., de Vegt, F., 2011. The healthy donor effect: a matter of selection bias and confounding. Transfusion 51 (9), 1883–1885. https://doi.org/10.1111/j.1537-2995.2011.03270.x.

Bech, Per, Timmerby, N., Martiny, K., Lunde, M., Soendergaard, S, 2015. Psychometric evaluation of the Major Depression Inventory (MDI) as depression severity scale using the LEAD (Longitudinal Expert Assessment of All Data) as index of validity. BMC Psychiatry 15 (1). https://doi.org/10.1186/s12888-015-0529-3.

Bech, P., Rasmussen, N.A., Olsen, L.R., Noerholm, V., Abildgaard, W., 2001. The sensitivity and specificity of the Major Depression Inventory, using the Present State Examination as the index of diagnostic validity. J. Affect. Disord. https://doi.org/10.1016/S0165-0327(00)00309-8.

Bjelland, I., Krokstad, S., Mykletun, A., Dahl, A.A., Tell, G.S., Tambs, K., 2008. Does a higher educational level protect against anxiety and depression? The HUNT study. Soc. Sci. Med. 66 (6), 1334–1345. https://doi.org/10.1016/j.socscimed.2007.12.019. *1982*.

Blanco, C., Vesga-López, O., Stewart, J.W., Liu, S.M., Grant, B.F., Hasin, D.S., 2012. Epidemiology of major depression with atypical features: results from the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC). J. Clin. Psychiatry 73 (2), 224–232. https://doi.org/10.4088/JCP.10m06227.

Bremner, J.D., Moazzami, K., Wittbrodt, M.T., Nye, J.A., Lima, B.B., Gillespie, C.F., Rapaport, M., Pearce, B., Shah, A., Vaccarino, V., 2020. Diet, Stress and Mental Health. Nutrients 12 (8). https://doi.org/10.3390/nu12082428.

Bukh, J.D., Bock, C., Vinberg, M., Kessing, L.V., 2013. The effect of prolonged duration of untreated depression on antidepressant treatment outcome. J. Affect. Disord. https://doi.org/10.1016/j.jad.2012.07.008.

Burgdorf, K.S., Simonsen, J., Sundby, A., Rostgaard, K., Pedersen, O.B., Sørensen, E., Nielsen, K., Bruun, M., Frisch, M., Edgren, G., Erikstrup, C., Hjalgrim, H., Ullum, H., 2017. Socio-demographic characteristics of Danish blood donors. PLoS ONE. https://doi.org/10.1371/journal.pone.0169112.

Cavanagh, A.B.A., Wilson, C.J., Kavanagh, D.J., Caputi, P., 2017. Differences in the expression of symptoms in men versus women with depression: a systematic review and meta-analysis. Harv. Rev. Psychiatry 25 (1), 29–38.

Ceresa, A., Esposito, C.M., Surace, T., Legnani, F., Cirella, L., Cetti, D., Paolo, Di, l, M., Nosari, G., Zanelli Quarantini, F., Serati, M., Ciappolino, V., Caldiroli, A., Capuzzi, E., Buoli, M, 2022. Gender differences in clinical and biochemical parameters of patients consecutively hospitalized for unipolar depression. Psychiatry Res 310, 114476. https://doi.org/10.1016/J.PSYCHRES.2022.114476.

Didriksen, M., Allen, R.P., Burchell, B.J., Thørner, L.W., Rigas, A.S., di Angelantonio, E., Nielsen, M., Jennum, P., Werge, T., Erikstrup, C., Pedersen, O., Nielsen, K., Bruun, M., Burgdorf, K., Sørensen, E., Ullum, H. (2018). Restless legs syndrome is associated with major comorbidities in a population of Danish blood donors. *Sleep Med.*, 45, 124–131. https://doi.org/10.1016/J.SLEEP.2018.02.007.

Didriksen, M., Thørner, L.W., Larsen, M.A.H., Sørensen, E., Burgdorf, K., Mikkelsen, S., Rostgaard, K., Banasik, K., Pedersen, O., Erikstrup, C., Nielsen, K., Bruun, M., Hjalgrim, H., Ullum, H., 2021. The impact of health-related quality of life and depressive symptoms on blood donor career—Results from the Danish blood donor study. Transfusion 61 (5), 1479–1488. https://doi.org/10.1111/trf.16336.

Ellervik, C., Kvetny, J., Christensen, K.S., Vestergaard, M., Bech, P., 2014. Prevalence of depression, quality of life and antidepressant treatment in the Danish General Suburban Population Study. Nord. J. Psychiatry 68 (7), 507–512. https://doi.org/10.3109/08039488.2013.877074.

Esposito, C.M., Buoli, M., 2020. The biological face of melancholia: are there any reliable biomarkers for this depression subtype? J. Affect. Disord. 266, 802–809. https://doi.org/10.1016/j.jad.2020.02.036. Elsevier B.V.

Fluharty, M., Taylor, A.E., Grabski, M., & Munafò, M.R. (2017). The Association of Cigarette Smoking With Depression and Anxiety: a Systematic Review. *Nicotine Tobacco Res.*, 19(1), 3–13. https://doi.org/10.1093/ntr/ntw140.

Greenberg, P.E., Fournier, A.A., Sisitsky, T., Pike, C.T., Kessler, R.C., 2015. The economic burden of adults with major depressive disorder in the United States (2005 and 2010). Journal of Clinical Psychiatry 76 (2), 155–162. https://doi.org/10.4088/JCP.14m09298.

Grynderup, M.B., Mors, O., Hansen, Å.M., Andersen, J.H., Bonde, J.P., Kærgaard, A., Kærlev, L., Mikkelsen, S., Rugulies, R., Thomsen, J., Kolstad, H.A., 2012. A two-year follow-up study of risk of depression according to work-unit measures of psychological demands and decision latitude. Scand J Work Environ Health 38 (6), 527–536. https://doi.org/10.5271/sjweh.3316.

Halfin, A., 2007. Depression: the benefits of early and appropriate treatment. Am. J. Managed Care 13 (11 SUPPL. 4).

Hansen, T.F., Banasik, K., Erikstrup, C., Pedersen, O.B., Westergaard, D., Chmura, P.J., Nielsen, K.J., Thørner, L., Hjalgrim, H., Paarup, H., Ærsen, M., Petersen, M., Jennum, P., Andersen, S., Nyegaard, M., Jemec, G., Olesen, J., Werge, T., Johansson, P., Sørensen, E., Brunak, S., Ullum, H., Burgdorf, K.S., 2019. DBDS Genomic Cohort, a prospective and comprehensive resource for integrative and temporal analysis of genetic, environmental and lifestyle factors affecting health of blood donors. BMJ Open 9 (6), e028401. https://doi.org/10.1136/bmjopen-2018-028401.

Han, S.Y.S., Cooper, J.D., Ozcan, S., Rustogi, N., Penninx, B.W.J.H., & Bahn, S. (2019). Integrating proteomic, sociodemographic and clinical data to predict future depression diagnosis in subthreshold symptomatic individuals. *Transl. Psychiatry*, 9 (1), 277. https://doi.org/10.1038/s41398-019-0623-2.

Harald, B., Gordon, P., 2012. Meta-review of depressive subtyping models. J. Affect. Disord. 139, 126–140. https://doi.org/10.1016/j.jad.2011.07.015.

Keyes, K.M., Allel, K., Staudinger, U.M., Ornstein, K.A., Calvo, E., 2019. Alcohol consumption predicts incidence of depressive episodes across 10 years among older adults in 19 countries. Int. Rev. Neurobiol. 148, 1–38. https://doi.org/10.1016/bs.irn.2019.09.001.

Kuehner, C., 2017. Why is depression more common among women than among men? The Lancet Psychiatry 4 (2), 146–158. https://doi.org/10.1016/S2215-0366(16)30263-2.

Lamers, F., Vogelzangs, N., Merikangas, K.R., de Jonge, P., Beekman, A.T.F., Penninx, B.W.J.H., 2013. Evidence for a differential role of HPA-axis function, inflammation and metabolic syndrome in melancholic versus atypical depression. Mol. Psychiatry 18 (6), 692–699. https://doi.org/10.1038/mp.2012.144.

Lamers, F., Milaneschi, Y., Vinkers, C.H., Schoevers, R.A., Giltay, E.J., Penninx, B.W.J.H., 2020. Depression profilers and immuno-metabolic dysregulation: longitudinal results from the NESDA study. Brain Behav. Immun. 88, 174–183. https://doi.org/10.1016/j.bbi.2020.04.002.

Llorente, J.M., Oliván-Blázquez, B., Zuñiga-Antón, M., Masluk, B., Andrés, E., García-Campayo, J., Magallón-Botaya, R., 2018. Variability of the Prevalence of Depression in Function of Sociodemographic and Environmental Factors: ecological Model. Front. Psychol. 9, 2182. https://doi.org/10.3389/fpsyg.2018.02182.

Marcus, S.M., Kerber, K.B., Rush, A.J., Wisniewski, S.R., Nierenberg, A., Balasubramani, G.K., Ritz, L., Kornstein, S., Young, E., Trivedi, M.H., 2008. Sex differences in depression symptoms in treatment-seeking adults: confirmatory analyses from the Sequenced Treatment Alternatives to Relieve Depression study. Compr. Psychiatry 49 (3), 238–246. https://doi.org/10.1016/j.comppsych.2007.06.012.

Olsen, L.R., Mortensen, E.L., Bech, P., 2004. Prevalence of major depression and stress indicators in the Danish general population. Acta Psychiatr Scand. https://doi.org/10.1046/j.0001-690X.2003.00231.x.

Pedersen, C.B., 2011. The Danish civil registration system. Scand. J. Public Health. https://doi.org/10.1177/1403494810387965.

Pedersen, O.B., Erikstrup, C., Kotzé, S.R., Sørensen, E., Petersen, M.S., Grau, K., Ullum, H., 2012. The Danish Blood Donor Study: a large, prospective cohort and biobank for medical research. Vox Sang. 102, 271. https://doi.org/10.1111/j.1423-0410.2011.01553.x.

Rice, S., Seideler, Z., Kealy, D., Ogrodniczuk, J., Zajac, I., Oliffe, J., 2022. Men's depression, externalizing, and DSM-5-TR: primary signs and symptoms or co-occuring symptoms? Harv. Rev. Psychiatry 30 (5), 317–322. https://doi.org/10.1097/HRP.0000000000000346.

Rigas, Andreas Stribolt, Sørensen, C.J., Pedersen, O.B., Petersen, M.S., Thørner, L.W., Kotzé, S., Sørensen, E., Magnussen, K., Rostgaard, K., Erikstrup, C., Ullum, H, 2014. Predictors of iron levels in 14,737 Danish blood donors: results from the Danish Blood Donor Study. Transfusion. https://doi.org/10.1111/trf.12518.

Rigas, A.S., Skytthe, A., Erikstrup, C., Rostgaard, K., Petersen, M.S., Hjalgrim, H., Ullum, H., Kyvik, K., Pedersen, O.B., 2019a. The healthy donor effect impacts self-reported physical and mental health - results from the Danish Blood Donor Study (DBDS). Transfus. Med. 29 (Suppl 1), 65–69. https://doi.org/10.1111/tme.12478.

Rigas, A.S., Pedersen, O.B., Magnussen, K., Erikstrup, C., Ullum, H., 2019b. Iron deficiency among blood donors: experience from the Danish Blood Donor Study and from the Copenhagen ferritin monitoring scheme. Transfusion Med. 29, 23–27. https://doi.org/10.1111/tme.12477.

Steenstrup, T., Pedersen, O.B., Hjelmborg, J., Skytthe, A., Kyvik, K.O., 2013. Heritability og Health-Related Quality of Life: SF-12 Summary Scores in a Population-based Nationwide Twin Cohort. Twin Res. Hum. Genetics 16, 670–678. https://doi.org/10.1017/thg.2013.21.

Vetter, J.S., Spiller, T.R., Cathomas, F., Robinaugh, D., Brühl, A., Boeker, H., Seifritz, E., Kleim, B., 2021. Sex differences in depressive symptoms and their networks in a treatment-seeking population – a cross sectional study. J Affect Disord 278, 257–362. https://doi.org/10.1016/j.jad.2020.08.074.

Vulser, H., Wiernik, E., Hoertel, N., Thomas, F., Pannier, B., Czernichow, S., Hanon, O., Simon, J., Danchin, N., Limosin, F., Lemogne, C., 2016. Association between depression and anemia in otherwise healthy adults. Acta Psychiatr. Scand. 134 (2), 150–160. https://doi.org/10.1111/acps.12595.

Wang, K., Liu, Y., Ouedraogo, Y., Wang, N., Xie, X., Xu, C., Luo, X., 2018. Principal component analysis of early alcohol, drug and tobacco use with major depressive disorder in US adults. J. Psychiatr. Res. 100, 113–120. https://doi.org/10.1016/j.jpsychires.2018.02.022.

World Health Organization. (2017). Depression and Other Common Mental disorders: Global Health Estimates. World Health Organization. https://doi.org/CCBY-NC-SA3.0IGO.

Xu, J., Wang, J., Wimo, A., Qiu, C., 2016. The economic burden of mental disorders in China, 2005-2013: implications for health policy. BMC Psychiatry 16 (1). https://doi.org/10.1186/s12888-016-0839-0.