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**General practitioners' drug treatment for depression by patients'  
educational level: registry-based study**

**Running title: antidepressant treatment and educational level**

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## ABSTRACT

**Background:** Antidepressant drugs are often prescribed in general practice. Evidence is conflicting on how patient education influences antidepressant treatment.

**Aim:** To investigate the association between educational attainment and drug treatment in adult patients with a new depression diagnosis, and to what extent gender and age influence the association.

**Design and setting:** Nationwide registry-based cohort study, Norway, 2014-2016.

**Method:** The study comprised all residents of Norway born before 1996 and alive in 2015. We obtained information on all new depression diagnoses in general practice in 2015 (**Primary Care Database**) and data on all dispensed depression medication (Norwegian Prescription Database) 12-months after the date of diagnosis. Independent variables were education, gender, and age. Associations with drug treatment were estimated using a Cox proportional hazard model, **for genders separately.**

**Results:** Out of 49,967 patients with new depression (61.6% women), 15,678 were dispensed drugs (30.4% women, 33.0% men). Highly educated women were less likely to receive medication (**Hazard Ratio** (HR) =0.93, 95% CI (0.88 – 0.98)) than women with low education. No such differences appeared among men. Women aged 20-29 were more likely to be treated with drugs than those aged 30-59, and women aged 70+ were more likely to receive drugs (HR=1.65, (1.54 – 1.77)) than those aged 20-29. The pattern was similar but less pronounced for men.

**Conclusion:** Educational differences in antidepressant therapy among women may reflect different treatment approaches that clinicians should be aware of to avoid unintended variation. Reasons for this variation and consequences for quality of treatment should be explored.

**Keywords:** antidepressive agents; depression; educational status; general practice; health services research; large database research.

### How this fits in

Medication for the treatment of depression is often prescribed by GPs, but little is known about factors that influence GP depression care. This study shows that highly educated women with a new depression diagnosis receive less medication than women with low education, while no such differences appear among men. Further, the youngest and the oldest patients are most likely to receive antidepressant drugs. These differences may reflect

different depression care approaches that clinicians should be aware of to avoid inequity in treatment.

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## INTRODUCTION

The use of antidepressant drugs has increased substantially during the 1990s and early 2000s.<sup>1-3</sup> With respect to prevalence of depression, studies indicate that women,<sup>4,5</sup> older people,<sup>6-8</sup> and lower socioeconomic groups<sup>9</sup> are at increased risk. Moreover, women are more likely to consult their general practitioner (GP) for depression compared to men<sup>10</sup>. Whether drug use is equally distributed across population groups, such as higher and lower educated, is poorly examined and findings so far are inconsistent.<sup>11-13</sup> With respect to gender and age, some studies indicate that GPs prescribe more depression drug therapy to women and older people than to men and younger people.<sup>14,15</sup> However, there is a lack of studies that use a new depression diagnosis to confirm this trend.

GPs play a key role in providing health services to patients with depression. According to guidelines, talking therapy by GP is the first choice of treatment for mild depression.<sup>16,17</sup> With increased severity, talking therapy may be combined with medication.<sup>16</sup> In Norway, about 80% of antidepressant prescriptions are issued by a GP.<sup>14</sup> Large registry-based studies with complete data on diagnoses, depression medication and population demography may increase the knowledge and awareness about variation in health care provision to patients with depression.

The aim of this study was to investigate the association between educational attainment and drug treatment in adult patients with a new diagnosis of depression, and to what extent gender and age influence the association.

## METHODS

### Design

We conducted a nationwide registry-based cohort study with data from the *Norwegian GP-DEP Study*, which investigates pathways of depression care in general practice. Our cohort comprised all individuals with a new depression diagnosis in general practice in 2015. The cohort was examined regarding dispensing of medication for depression in the 12 months after the first date of depression diagnosis (index date) in 2015.

### Data sources

Information from national registries was linked at the individual level, using the unique personal identity number (encrypted) assigned to all residents of Norway. All data was stored and analysed at a safe server at the University of Bergen.

The Control and reimbursement of health care claims (KUHR) database stores data on all fee-for-service claims from GPs. For each encounter, the claims contain a GP- and patient-identifier, date of contact, and one or more diagnoses according to the International Classification of Primary Care 2<sup>nd</sup> version (ICPC-2).

The Norwegian prescription database (NorPD) stores information on all prescription drugs dispensed to patients treated in ambulatory care.<sup>18</sup> For each prescription, NorPD contains an encrypted prescriber- and patient-identifier, date of dispensing, generic drug information (Anatomical Therapeutic Chemical (ATC) code), and any reimbursement code. NorPD lacks information at individual level on medication dispensed to people staying in hospitals or nursing homes.

The Norwegian Patient Registry (NPR) comprises information on all patient contacts with secondary health care, with diagnoses according to the International Classification of Disease 10<sup>th</sup> revision (ICD-10).

The National Education Database stores information on the highest level of completed education.

The Population Registry contains information on gender, year of birth, death and emigration.

### **Study population**

The source population comprised all inhabitants of Norway born before 01.01.1996 and alive 01.01.2015 (4,017,989 individuals). First, we identified all individuals with a depression diagnosis in general practice (GP-consultation with the ICPC-2 code P76 Depression in KUHR) in 2015 (N=124,948). Second, to establish a cohort of patients with a *new* diagnosis of depression, we conducted washout of 74,981 patients with a diagnosis of depression in general practice (P76 in KUHR) and/or secondary care (ICD-10 codes F32, F33, F34 or F41.2 in NPR) and/or dispensed drug treatment for depression (NorPD) during 12-months *prior to index date*. The resulting study population comprised 49,967 individuals (Figure 1).

### **Independent variables**

The National Education Database is based on the International Standard Classification of Education.<sup>19</sup> We recoded 11 levels into three categories: low (primary school (Grades 1-7)

and lower secondary school (Grades 8-10) or less), medium (13 years, upper-secondary school) and high (>13 years, university and higher education). We recoded patient age into decennial categories.

### **Outcome**

From NorPD we included all medications reimbursed for the treatment of depression: antidepressants (ATC code N06A), selected antiepileptic drugs (N03A) and selected antipsychotic drugs (N05A), dispensed during 12-months follow-up after index date (yes, no). Number of days from index date to first drug dispensing, was categorised as 0-7, 8-31, 32-183, and 184-365 days. Since drug treatment was initiated by a GP in 86% of the cases, we use the term “GP drug treatment”.

### **Statistical analysis**

Descriptive statistics was used to examine the distribution of antidepressants, antiepileptics and antipsychotics among the patients treated with drugs, given by numbers and percentages. Dispensing of medication and time interval from index date to first drug dispensing was provided by numbers and percentages, by educational level, gender, and age category. The associations between drug dispensing and education, gender and age were examined by chi square test. Further, Cox proportional hazard models were used to estimate the likelihood of being dispensed medication for the independent variables education, gender and age. Interactions between education and gender, and between education and age, in the association with drug dispensing were tested in separate Cox proportional hazard models. Follow-up was defined in days from index date to first drug dispensing, and individuals were censored at the time of death, emigration, or end of follow-up, whichever occurred first. The results from the final model were presented stratified by gender (due to interaction), both crude and adjusted, as hazard ratios (HR) with 95% confidence intervals (CI). Reference groups were low education and age group 20-29 year.

The association between educational level and time to first drug dispensing was illustrated by Kaplan-Meier survival curves, and a pairwise log rank test was used to test the equality of the distribution of the survival curves between different education levels, for gender separately. Missing data on education (1.1%) were excluded in the analyses. For all statistical analyses, we used  $\alpha = 0.05$  as significance level. SPSS software version 25.0.0.2 was used (PASW Statistics for Windows, SPSS Inc., Chicago, IL, USA).

## RESULTS

The study population comprised 49,967 individuals with a new depression diagnosis in 2015, with a mean age of 44.4 (standard deviation, 16.2) years, 21,421 (61.6%) women and 19,192 (38.4%) men. Among all patients, 30.1 % had low education, 40.1% medium, and 28.1% high (Table 1). The study population comprised a relatively higher proportion of men and younger age groups compared to the washed-out population (Supplementary Table 1).

Among the study population, 15,678 (31.4%) were dispensed depression drugs during the 12-month follow-up, 9,354 (30.4%) women and 6,324 (33.0%) men (Table 1). Of those receiving medication, 85.2% were dispensed antidepressants only, 4.8 % antipsychotics only and 1.2% antiepileptics only, while 8.8% received drugs from two or three therapeutic groups (Table 2). Selective serotonin reuptake inhibitors made up for 66% of the antidepressants (N06A) dispensed.

Medication was more commonly provided to those with low educational level versus high, to men versus women and to those aged 20-29 or 70+ versus other age groups, Table 1.

Altogether 8,809 patients collected medication within one week of index date, corresponding to 56% (8,809/1,5678) of patients treated with drugs, and 17.6% (8,809/49,967) of the total study population, respectively.

Due to a significant interaction between education and gender ( $P=0.010$ ), the Cox proportional hazard model was performed for men and women separately. Women with high and medium education were less likely to receive drugs (crude HR=0.94, (0.90 – 0.99) and HR=0.86, (0.81 – 0.90), respectively) compared to women with low education (reference), Table 3. The age adjusted estimates were less pronounced but still significant for highly educated women. Among men there was no association between drug treatment and education. There was no interaction between gender and age. Women aged 20-29 were more likely to be treated with medication compared to those aged 30 to 59, and women aged 70+ were even more likely to receive medication (HR=1.65, 95% CI (1.54 – 1.77)) than those aged 20-29. The pattern was similar but less pronounced for men.

Figure 2 illustrates the distribution of survival curves for time to first drug dispensing.

Women (Figure 2a) with high education were dispensed depression drugs to a lesser extent



and later after index date, compared to those with low or medium education ( $P \leq 0.001$  for both groups). There was also a different distribution between medium and low educated women ( $P=0.018$ ). Highly educated men (Figure 2b) had a different distribution of drug dispensing than men with medium education ( $P=0.013$ ).

## **DISCUSSION**

### **Summary**

In a nationwide cohort of patients with a new diagnosis of depression, we found a gendered pattern in the occurrence of depression and in the likelihood of receiving medication by educational level. While GP-diagnosed depression was considerably more prevalent among women, the proportion being treated with drugs was higher among men. Gender modified the relation between education and medication; hence all analyses were performed separately for men and women. A novel finding was that highly educated women with new depression were significantly less likely to receive medication than lower educated women, even after adjusting for age. No educational differences were found for men. Finally, the youngest and the oldest patients were the age-groups most likely to receive depression drugs.

### **Strengths and limitations**

The main strength of this study is the use of complete registry data from the publicly subsidised primary care services in Norway. Linkage of data from five national registries at the individual level provides a unique source of information, eliminating recall bias and selection bias.

Information on GP-diagnosed depression is another strength. A new depression diagnosis was defined as a GP-consultation with the ICPC-2 code P76, after a 1-year washout period. However, the individual GPs set the diagnosis and the KUHR database has no formal control on diagnostic categories. Differing coding behavior may therefore challenge the internal validity. However, potential misclassification by the GP would be non-differential and distributed randomly across population groups. Another limitation is lack of information on severity of depression, as ICPC-2 does not allow for such grading. Severity probably influences GPs' decisions to initiate drug treatment. On the other hand, variation in severity is most likely also distributed evenly across patient educational level, gender and age.

The NorPD contains complete data on all prescription drugs *dispensed*. Although we may have slightly underestimated the prevalence of *prescribed* medication for depression, the use of drug dispensing data is recognised as an acceptable proxy in epidemiological studies.<sup>20</sup> Low out-of-pocket payment in Norway makes medication for depression easily available, and we thus believe that primary non-compliance is low and evenly distributed across population groups. To strengthen the internal validity, we have considered drugs reimbursed for the treatment of depression only, eliminating e.g. SSRIs for anxiety disorder and tricyclic antidepressants for adjuvant pain therapy.

### **Comparison with existing literature**

The prevalence of drug therapy for new depression found in our study (one of three patients) is considerably lower than antidepressant prescription rates of 45%-75% reported in studies from European countries.<sup>21-23</sup> This discrepancy may be due to use of a new diagnosis of depression, a strict definition of depression medication, and the use of drug dispensing data in our study. Half of the patients who started on drug treatment collected medication within one week after index date. This finding is in line with studies in the Netherlands and Sweden examining the time interval from depression diagnosis to initiation of drug treatment.<sup>22,23</sup>

Turning to gender, a Swedish registry study also including only newly diagnosed patients with depression found a slightly greater proportion of men than women receiving antidepressant drugs,<sup>23</sup> in line with our findings. The lower proportion of women using depression drugs may be related to gendered preferences; women preferring talking therapy, men drug treatment.<sup>24-26</sup> On the other hand, GPs may initiate talking therapy to women due to a preconception that they are more inclined to conversation.

A study in the UK among people aged 55 years and older showed that treatment rates with antidepressants were high for those recorded with a new depression diagnosis but varied little by age.<sup>8</sup> The present study indicates that the youngest and the oldest patients were most commonly prescribed medication. Higher prescription rates for older people may be an expression of unwarranted variation, since studies suggest that elderly judge talking therapy more favorably than medication.<sup>27,28</sup> GPs should be aware of older patients' increased risk of polypharmacy and adverse side effects.<sup>29</sup> This practice may nevertheless be due to brief GP encounters with focus on somatic conditions,<sup>27</sup> or to limited access to secondary mental health care.<sup>31</sup>

Depression is more prevalent among people with low socioeconomic status (SES) compared to those better off.<sup>9</sup> Previous studies investigating the relationship between education and antidepressant use have demonstrated divergent findings. In line with our results, a registry-based study in Sweden showed that poorly educated people received more prescriptions of antidepressants than those with higher education; the educational gradient being somewhat stronger among women than among men.<sup>12</sup> Accordingly, Packness and colleagues in Denmark found that higher educated groups with no/few self-reported symptoms of depression were less likely to use medication, however, no associations were found among people with more pronounced symptoms.<sup>13</sup> In contrast, Kivimäki and colleagues found lesser antidepressant use among men with lower education compared to men with higher education in Finland, while such differences were not seen in women.<sup>11</sup> Finally, two studies conducted in Denmark and one in Australia showed no association between education and antidepressant use.<sup>32-34</sup> The conflicting results in these studies could be due to different study populations and measures of educational status, or to cross-national differences in access to treatment among disadvantaged people. In contrast to the current study, none of these studies comprised information on new depression diagnoses made by a GP.

Socioeconomic variation in antidepressant use found in this study may reflect an unintended bias by the GP letting SES influence prescription of medication,<sup>34</sup> differential patient preferences supported by the GP, or a combination. One may speculate whether GPs prescribe drugs rather than provide talking therapy to patients they perceive as less educated, or whether better educated patients are more assertive about having non-pharmacological therapy. A survey among patients in GP waiting rooms in Norway showed that lower educational level was associated with greater preference for medication.<sup>35</sup> The association between educational level and drug treatment found in our study among women only, may suggest that highly educated women are more skeptical to medication in general. This may apply particularly to younger women since older women in the study population were less educated.

### **Implications for research and/or practice**

The results of our study support an association between drug treatment for new depression and patient gender, education and age. Highly educated women received less medication than women with low education, and no such differences appeared among men. Educational differences among women may reflect different treatment approaches that clinicians should be

aware of to avoid unintended variation. Qualitative studies or register studies with long-time observation of treatment outcomes are needed to further explore the observed variation across educational levels, its reasons and implications for the quality of depression treatment.

## DECLARATIONS

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**Ethical Approval:** Regional Committee for Medical and Health Research Ethics (2017/934). Norwegian Data Inspectorate (17/01372).

**Competing interests:** The authors declare that they have no competing interests.

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**Data availability:** The data underlying this article were provided by national health- and population registries, by permission. The data cannot be shared due to restrictions by the Norwegian Data Protection Authority.

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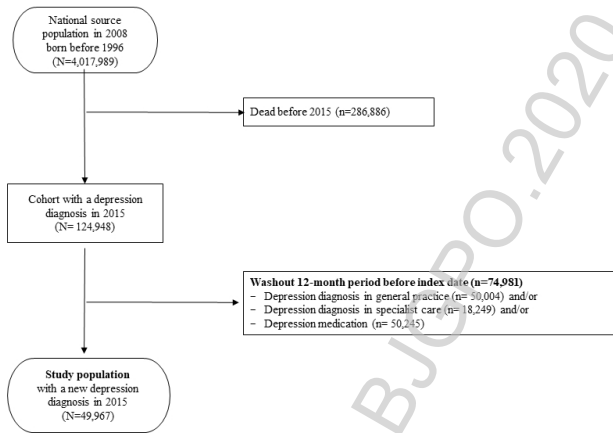


Figure 1. Flow chart illustrating the definition of the study population; patients in Norway, aged 20 years and older, with new depression diagnosis in 2015 (N = 49,967).

338x190mm (96 x 96 DPI)



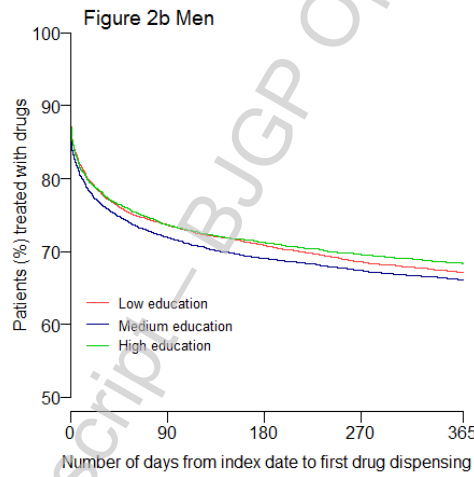
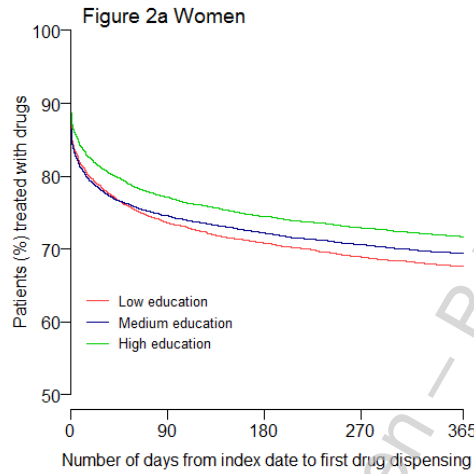


Figure 2. The association between educational level and number of days from index date to first drug dispensing (Kaplan Meier survival curves) for patients in Norway, aged 20 years and older with a new depression diagnosis in 2015 (N=49 967).

276x392mm (72 x 72 DPI)

Table 1. Drug treatment for patients with a new depression diagnosis in 2015, and time from date of diagnosis to first drug dispensing, by education, gender and age (N=49,967)

	Patients treated with drugs for depression								
	Total	No		Yes		Number of days from index date to first drug dispensing			
		N	N	%	N	%	0-7 %	8-31 %	32-183 %
<b>Educational level</b>									
Low	15,024	10,130	67.4	4,894	32.6	17.8	4.4	7.1	3.3
Medium	20,015	13,624	68.1	6,391	31.9	18.6	4.3	6.2	2.8
High	14,380	10,168	70.7	4,212	29.3	16.1	3.9	6.5	2.7
Missing	548								
<b>Gender</b>									
Women	30,775	21,421	69.6	9,354	30.4	17.2	4.0	6.4	2.8
Men	19,192	12,868	67.0	6,324	33.0	18.3	4.7	6.9	3.1
<b>Age group, years</b>									
20-29	10,975	7,434	67.7	3,541	32.2	17.0	4.6	7.3	3.4
30-39	10,157	7,215	71.0	2,942	29.0	14.9	4.2	6.9	3.0
40-49	10,951	7,736	70.6	3,215	29.4	15.2	4.5	6.8	2.9
50-59	8,921	6,326	70.9	2,595	29.1	16.0	4.1	6.0	3.0
60-69	5,136	3,548	69.1	1,588	30.9	19.9	3.4	5.6	2.0
70+	3,827	2,030	53.0	1,797	47.0	34.1	4.5	5.5	2.8
<b>Total</b>	49,967	34,289	68.6	15,678	31.4	17.6	4.3	6.6	2.9

Educational level: Low (primary school (Grades 1-7) and lower secondary school (Grades 8-10) or less), medium (13 years, upper-secondary school) and high (>13 years, university and higher education)

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Table 2. Distribution of drug groups dispensed to patients with a new depression diagnosis in 2015 and treated with medication (N=15,678)

	N	%
Antidepressant drug only	13,356	85.2
Antipsychotic drug only	745	4.8
Antiepileptic drug only	183	1.2
Antidepressant + Antipsychotic	1,130	7.2
Antidepressant + Antiepileptic	113	0.7
Antipsychotic + Antiepileptic	56	0.4
Antidepressant + Antipsychotic + Antiepileptic	95	0.6
Total	15,678	100

Medications reimbursed for the treatment of depression in Norway (ATC code):

Antidepressants (N06A)

- Non-selective monoamine reuptake inhibitors (N06AA): desipramine, imipramine, imipramine oxide, clomipramine, opipramol, trimipramine, lofepramine, debenzepin, amitryptilin, nortyptiline, doxepin, iprindole, melitracen, butrityline, dosulepin, amoxapine, demetacrine, amineptine, maprotiline, quinupramine.
- Selective serotonin reuptake inhibitors (N06AB): zimeldine, fluoxetine, citalopram, paroxetine, sertraline, alaproclate, fluvoxamine, etoperidone, escitalopram.
- Monoamine reuptake inhibitors (N06AG): moclobemide, toloxatone.
- Other antidepressants (N06AX): oxitriptan, tryptophan, mianserin, nomifensine, trazodone, nefazodone, minaprine, bifemelane, viloxazine, oxaflozane, mirtazapine, bupropion, medifoxamine, tianeptine, pivagabine, venlafaxine, milnacipran, reboxetine, gepirone, duloxetine, agomelatine, desvenlafaxine, vilazodone, hyperici herba, vortioxetine.

Antiepileptic drugs (N03A): valproic acid, carbamazepine, lamotrigine.

Antipsychotic drugs (N05A): ziprasidone, loxapine, olanzapine, quetiapine, asenapine, risperidone, aripipazole, lithium.

Table 3. Likelihood of receiving drug treatment (Hazard ratio, 95% CI) among patients with a new depression diagnosis in 2015, by education and age; stratified by gender (N=49,967)

	N	Drug treatment		Unadjusted		Adjusted*	
		n	%	HR	95% CI	HR	95% CI
<b>Women</b>							
<b>Educational level**</b>							
Low	8,572	2,775	32.4	1		1	
Medium	11,829	3,622	30.6	0.94	(0.90 – 0.99)	0.97	(0.92 - 1.02)
High	10,053	2,844	28.3	0.86	(0.81 – 0.90)	0.93	(0.88 – 0.98)
<b>Age group, years</b>							
20-29	6,802	2,132	31.3	1		1	
30-39	6,190	1,714	27.7	0.87	(0.81 – 0.92)	0.87	(0.82 – 0.93)
40-49	6,577	1,827	27.8	0.87	(0.82 – 0.93)	0.87	(0.82 - 0.93)
50-59	5,338	1,466	27.5	0.86	(0.81 – 0.92)	0.86	(0.81 – 0.92)
60-69	3,161	969	30.7	0.99	(0.92 – 1.07)	1.00	(0.92 – 1.07)
70+	2,707	1,246	46.0	1.66	(1.66 – 1.55)	1.65	(1.54 – 1.77)
<b>Men</b>							
<b>Educational level**</b>							
Low	6,452	2,119	32.8	1		1	
Medium	8,186	2,769	33.8	1.04	(0.98 – 1.02)	1.04	(0.98 – 1.10)
High	4,327	1,368	31.6	0.96	(0.90 – 1.03)	0.97	(0.90 – 1.04)
<b>Age group, years</b>							
20-29	4,173	1,409	33.8	1		1	
30-39	3,967	1,228	31.0	0.90	(0.84 – 0.98)	0.90	(0.84 – 0.98)
40-49	4,374	1,388	31.7	0.93	(0.86 – 1.00)	0.93	(0.86 – 1.01)
50-59	3,583	1,129	31.5	0.92	(0.85 – 1.00)	0.92	(0.85 – 1.00)

60-69	1,975	619	31.3	0.94	(0.85 – 1.03)	0.94	(0.85 – 1.03)
70+	1,120	551	49.2	1.70	(1.54 – 1.88)	1.70	(1.54 – 1.88)

Educational level: Low (primary school (Grades 1-7) and lower secondary school (Grades 8-10) or less), medium (13 years, upper-secondary school) and high (>13 years, university and higher education)

\*Adjusted for age and education, respectively.

\*\* Missing data on educational level for 321 women and 227 men.