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Late-life depression is associated with an increased risk of multimorbidity and polypharmacy.
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# Late-life depression and the association with multimorbidity and polypharmacy: a cross-sectional study

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## ABSTRACT

Background.
Late-life depression often coincides with chronic somatic diseases and, consequently, with polypharmacy, which may complicate medical treatment.
Objective.
To determine the associations between patients diagnosed with late-life depression in primary care and multimorbidity and polypharmacy.
Methods.
This cross-sectional observational study was performed using 2012 primary care data. Depressed patients aged ≥60 years were compared to age and gender matched patients diagnosed with other psychological diagnoses and mentally healthy controls. Morbidity and prescription data were combined, and regression analyses were performed for the associations between depression and chronic disease and chronic drug use.
Results.
We included 4477 patients; 1512 had a record of depression, 1457 of other mental health or psychological diagnoses and 1508 were controls. Depressed patients had a 16% [Prevalence Ratio (PR) 1.16; 95% confidence interval (95%

CI) 10%–24%] higher rate of chronic somatic disease and higher odds for multimorbidity (OR 1.55; 95% CI 1.33–1.81) compared with controls. No differences existed between depressed patients and patients with other psychological diagnoses. Compared with controls, depressed patients had a 46% (95% CI 39–53%) higher rate of chronic drug use and higher odds for polypharmacy (OR 2.89; 95% CI 2.41–3.47). Depressed patients also had higher rates of chronic drug use and higher odds for polypharmacy compared with patients with other psychological diagnoses (PR 1.26; OR 1.75; both $P < 0.001$).
Conclusions.
Late-life depression in primary care patients is associated with more chronic drug use, even beyond the increased rates of comorbid somatic diseases. General practitioners should consider medication reviews to prevent unnecessary drug-related problems in these patients.

## BACKGROUND

Depression and chronic somatic diseases are common in older adults. In primary care, major depression and multimorbidity (i.e., ≥2 comorbid chronic somatic diseases) have estimated 1-year prevalence rates of 10 and 65%, respectively (1,2). Depression and chronic somatic diseases frequently coincide (3). Chronic somatic diseases often require multiple drug treatments (4). Reports indicate that more than one third of people aged > 65 years use ≥5 drugs simultaneously (i.e. polypharmacy) (4), significantly increasing the risk of adverse drug-related events (5). Depression has been associated with chronic multiple drug use in hospital inpatients, even after adjusting for somatic comorbidity and antidepressant use (6). Also, depression is predominantly treated with an antidepressant (7), thereby contributing to polypharmacy, and potentially causing physical or cognitive impairment through anticholinergic and sedative (side-) effects of antidepressants (8).
Given that individuals diagnosed with depression and with chronic somatic diseases are usually treated in general practice (7), the association between depression and multimorbidity and polypharmacy need to be determined in that setting. Verifying these associations could help general practitioners identify patients at risk for adverse drug-related events. Therefore, the objectives of this study were 3-fold: to determine the associations between older individuals diagnosed with depression in primary care and multimorbidity, polypharmacy, and anticholinergic and sedative drug use; to identify whether these associations were independent of antidepressant use; and to identify whether the associations were specific for depression or for psychological distress in general.

## METHODS

### Design and setting

We conducted a cross-sectional observational study with data for 2012 from three sources: the Netherlands Institute of Health Services Research Primary Care Database (NIVEL-PCD), the Foundation of Pharmaceutical Statistics (SFK), and Statistics Netherlands (CBS). The NIVEL-PCD is a nationally representative database of routine data from the electronic medical records (EMRs) of patients registered at approximately 400 Dutch general practices (9). The EMRs contain

morbidity data for every consultation according to the diagnostic codes in the International Classification of Primary Care (ICPC), together with the patient's age and gender. Pharmacy dispensing data was obtained from the SFK, which collects data on all pharmacy-dispensed drugs from general practice and specialist care, including out-of-hours prescriptions (10); drugs are recorded according to the Anatomical Therapeutic Classification (ATC). The CBS holds and processes data on economic and societal characteristics of the Dutch population based on legal civil status and tax registers, so was used to collect sociodemographic data.

### Study population

NIVEL-PCD records for patients aged ≥60 years registered at participating general practices in 2012 were linked to individual SFK data by year of birth, gender, four-digit postal code, ATC code of prescribed drugs and its prescription and dispensing dates (11). To ensure matching, at least 50% of prescriptions from the NIVEL-PCD had to match the dispensing data from the SFK, with a lag period of 6 days allowed (11). Only patients with ≥1 prescriptions were included.

The composition of the study population out of the original population is presented in the Supplementary Table S1. Out of a total of 31693 patients registered at participating practices with successful linkage to their dispensing data, we identified three diagnostic groups for comparison. The first comprised all patients with either a recorded episode of a depressive disorder (ICPC code P76) or depressive symptoms (ICPC code P03) in 2012, irrespective of whether these were new or existing episodes. The second group comprised patients individually matched to the first by age and gender, who had no recorded episode of depression in 2012, but were diagnosed with any other new or existing psychological diagnosis (any other ICPC code in the 'P chapter', excluding P76/P03). The third group included control patients with no recorded mental health problems in 2012 (no ICPC code in the P chapter).

The recorded episode of depression in the first diagnostic group could well have coincided with comorbid psychological problems, as can be seen in Supplementary Table S2. Furthermore, patients recorded with other psychological problems not being depression, may have been diagnosed with multiple other psychological diagnoses.

## MEASURES

### Chronic diseases

We identified chronic diseases from ICPC codes based on a pre-defined list of 28 chronic diseases previously reported by the National Institute for Public Health and Environment (RIVM) (12). After excluding psychological disorders, since these were used to compose the diagnostic groups in our study, 20 chronic somatic diseases were identified (Table 1). We assessed the total number of chronic diseases per patient and whether multimorbidity (≥2 chronic diseases) was present (yes/no).

**[TABLE 1]**

### Chronic drugs

According to the definitions in the Dutch multidisciplinary guideline, *Polypharmacy in Older Patients*, 'chronic use' was defined as ≥4 prescriptions for a drug in a year

or use for ≥90 days, and 'polypharmacy' was defined as the chronic simultaneous use of ≥5 drugs with different ATC codes at the three-digit level (excluding dermatological medication [ATC chapter D]) (13). We calculated the total number of chronically used drugs per patient and whether polypharmacy was present (yes/no). Outcomes were assessed with and without antidepressants (ATC 'N06A').

**Drug burden Index**

To quantify the cumulative anticholinergic and sedative burden, we used the non-invasive Drug Burden Index (DBI) that takes the patient's dose into account (14). The DBI was calculated per patient, using the following formula:[14]$DBI = \sum D/(D+\delta)$; where $D$ was the daily drug dose and $\delta$ was the minimum recommended daily dose, according to Dutch standard references. Chronically used drugs with anticholinergic or sedative properties, as described previously (15), were included in the calculation. For each drug, the DBI could range from 0 to 1 depending on the value of δ. We determined the DBI with and without antidepressants being included.

**Confounders**

Age, gender and socioeconomic status (SES) were considered potential confounders. Age was determined as that on 1 January 2012. SES was a proxy measure based on four indicators (low income, mean income, proportion of low educated people, and proportion of unemployed), concerning the neighborhood in which patients live (16).

**Ethical considerations**

NIVEL handled all data in concordance with the Dutch Data Protection Act; a trusted third party, ZorgTTP, anonymized the data (17). Patients of participating general practices were informed about participation and offered the opportunity to opt out (17). The CBS was legally obliged to keep all data confidential. None of the information used could be traced to individuals.

**Statistical analysis**

We stratified our sample by diagnostic group and assessed differences by chi-square test for categorical variables, and by the Kruskal–Wallis test for continuous and count variables. If the overall Kruskal–Wallis test showed a statistically significant difference, we used the Mann–Whitney *U* test for post-hoc analysis to identify the groups with differences in pairwise comparisons. Despite the skewed distribution of our data, we decided to present means with standard deviations because of the large sample size and because this facilitated clinical interpretation.

To determine the associations between diagnostic group on one hand and the number of chronic diseases and chronic drugs on the other, we performed multivariable, multilevel, negative binomial regression analyses with patients (level 1) nested within general practices (level 2). Negative binomial regression analysis is a suitable approach to model over-dispersed count data. In these analyses, the number of chronic diseases or chronic drugs were entered as the dependent variable. Similarly, we modeled multimorbidity (yes/no) and polypharmacy (yes/no) as dependent variables in multivariable, multilevel, logistic regression analyses. Finally, we modeled DBI as the dependent variable in a multivariable, multilevel, linear regression analysis. In all analyses, the three matched diagnostic groups were entered as independent variable, with the mentally healthy control group as reference. All analyses were adjusted for age, gender and SES score nested within patients (level 1)

and patients nested within practice (level 2). Analyses with drugs as the dependent variable were also adjusted for the number of chronic diseases.
To determine whether associations were independent of antidepressant use, we repeated the analyses with drugs as dependent variable (number of drugs, polypharmacy and DBI) excluding antidepressant use. Subsequently, to assess whether any associations represented a specific effect of depression or of general psychological distress, we determined whether the respective coefficients differed with statistical significance.
We used Stata SE version 13.0 (StataCorp. 2013, College Station, TX) for all analyses. We present Prevalence Ratios (18), Odds Ratios, and coefficients for the respective regression analyses. Two-sided $P < 0.05$ were considered to indicate statistical significance. For post hoc descriptive analyses, $P < 0.017$ (Bonferroni correction: 0.05/3) were required for statistical significance to account for multiple comparisons.

## RESULTS

### Sample characteristics

Out of a total of 31 693 registered at participating practices with successful linkage to their dispensing data, we included 4477 patients aged ≥60 years (mean 67.9 years; 69.4% female). These included 1512 recorded with a depressive disorder or depressive symptoms who were matched with 1457 patients recorded with another psychological diagnosis and with 1508 controls. For the exact composition of the study population out of the potential eligible population registered at participating practices see Supplementary Data Table S1. Distribution of chronic somatic diseases differed significantly only for Parkinson's disease ($P < 0.001$) and COPD ($P < 0.001$), showing higher rates among depressed patients (Table 1). Distribution of P diagnoses is shown in the Supplementary Data Table S2.
The means and rates for all outcome measures were higher for depressed patients than for controls (Table 1). Concerning the number of chronic somatic diseases and the presence of multimorbidity, no difference existed between depressed patients and patients with other psychological diagnoses. However, depressed patients used more drugs chronically, had higher polypharmacy rates and had higher mean DBIs than patients with other psychological diagnoses, independent of antidepressant use.

### Chronic diseases

After adjustment for age, gender, SES score (all level 1), and general practice (level 2), depressed patients had a 16% higher rate [Prevalence Ratio 1.16; 95% confidence interval (95% CI) 10–24%] and patients with other psychological diagnoses had a 12% higher rate of chronic diseases (95% CI 5–18%) compared with controls (Table 2). The number of chronic diseases did not differ significantly between depressed patients and those with other psychological diagnoses ($P = 0.14$). Adjustment for practice level improved the model significantly ($P < 0.001$), 2.4% of the variance in the random model was explained by differences between practices.

**[TABLE 2]**

Logistic regression analysis for multimorbidity revealed higher odds ratios (OR) for depressed patients (OR 1.55; 95% CI 1.33–1.81) and for patients with other psychological diagnoses (OR 1.34; 95% CI 1.15–1.57) compared with controls

(Table 2). The odds for multimorbidity did not differ significantly between depressed patients and patients with other psychological diagnoses ($P = 0.06$). Adjustment for practice level improved the model significantly ($P < 0.001$), explaining 9.5% of the variance.

### Chronically used drugs

After adjustment for age, gender, SES score, number of chronic diseases (all level 1) and general practice (level 2), the rate for the number of chronically used drugs was 46% (95%CI 39%–53%) higher for depressed patients and 16% (95%CI 10%–22%) higher for patients with other psychological diagnoses compared with controls (table 3). Depressed patients had a 26% ($P < 0.001$) higher rate of chronic drug use than patients with other psychological diagnoses. Adjustment for practice level improved the model significantly ($P < 0.001$), explaining 1.3% of the variance.
Excluding antidepressants from the analyses decreased the differences between the three groups: compared with controls, chronic drug use was 24% (95% CI 18–30%; $P < 0.001$) and 13% (95% CI 7%–19%; $P < 0.001$) higher for depressed patients and patients with other psychological diagnoses, respectively. Compared to patients with other psychological diagnoses, depressed patients also had a 10% higher rate of chronic drug use other than antidepressants ($P < 0.001$). Adjustment for practice level improved the model significantly ($P < 0.001$), explaining 1.5% of the variance.
Compared with controls, depressed patients (OR 2.89; 95% CI 2.41–3.47) and patients with other psychological diagnoses (OR 1.66; 95% CI 1.38–2.00) were more likely to have polypharmacy (Table 3). Depressed patients were also more likely to have polypharmacy than patients with other psychological diagnoses (OR 1.75; $P < 0.001$). Adjustment for practice level improved the model significantly ($P < 0.001$), explaining 15.4% of the variance.
We found similar trends for polypharmacy after excluding antidepressants: compared with controls, the ORs were 1.99 (95% CI 1.66–2.40; $P < 0.001$) for depressed patients and 1.59 (95% CI 1.32–1.92; $P < 0.001$) for patients with other psychological diagnoses. Depressed patients also had higher odds for polypharmacy compared to patients with other psychological diagnoses, after excluding antidepressants (OR 1.25; $P = 0.01$). Adjustment for practice level improved the model significantly ($P < 0.001$), explaining 16.4% of the variance.

### Drug burden index

Depressed patients and patients with other psychological diagnoses had higher DBIs, regardless of antidepressant use, compared with controls ($P < 0.001$) (Table 3). This indicated the use of more drugs with anticholinergic and sedative characteristics. Moreover, depression was associated with a higher DBI, regardless of antidepressant use, compared with other psychological diagnoses ($P < 0.001$). In these analyses, adjustment for practice level again improved the model significantly ($P < 0.001$), explaining 5.3% of the variance in the model with antidepressants, and 3.8% of the variance in the model without antidepressants.

## DISCUSSION

### Summary of main findings

We found that, among older patients in primary care, those diagnosed with depression and with other psychological diagnoses had higher rates of chronic somatic disease compared with controls. Even after the adjustment for chronic

somatic disease rates, patients diagnosed with late-life depression used more drugs chronically and used more drugs with sedative and anticholinergic characteristics (i.e. they had a higher DBI) than either reference group. Moreover, these results were independent of antidepressant use. Patients with other psychological diagnoses also used more drugs chronically and had higher DBIs compared with controls. Of note, the originating general practices were associated with both chronic somatic diseases and chronic drug use, indicating that some characteristics of these practices might be associated with our outcome measures.

**Comparison with existing literature**

Our finding that depression in later life was associated with polypharmacy (excluding antidepressants) is consistent with that of a hospital-based study (6), in which polypharmacy was defined as the chronic use of ≥3 drugs (other than antidepressants and anxiolytics). To our knowledge, we are the first to show that this association is also present in primary care. A study in nursing homes also found an association between depressive symptoms and the use of ≥5 drugs, but included both antidepressants and non-chronic drugs (19). Our results add that patients diagnosed with late-life depression use more drugs chronically in primary care (excluding antidepressants), even after adjustment for the number of chronic somatic diseases. Depressed older patients had a higher DBI in this study, regardless of antidepressant use. Thus, there was chronic use of greater numbers of drugs with anticholinergic and sedative characteristics, which can impair physical function, activities of daily living, and cognition (8,14). However, no previous study has compared the DBI between depressed and non-depressed patients as we did. Researchers have suggested that the DBI should be used as a screening tool to identify patients at high risk of drug-related problems (15). Our results indicate that this might be even more relevant in depressed patients.

Consistent with earlier research, we also showed that late-life depression was associated with chronic somatic diseases (3,20). However, the 16% higher rate for depressed patients as compared with controls was smaller than we expected. Part of the explanation might be that our patients were included in primary care, a relatively healthy population compared with hospital inpatients for example. Furthermore, in univariate analyses (Table 1) the presence of the 20 included chronic diseases did not differ between the three diagnostic groups, except for Parkinson's Disease and COPD. In addition, due to the linkage between primary care records and pharmacy dispensing data only patients with ≥1 prescriptions could be included. Therefore, the controls did consult the GP with a somatic complaint for which at least one (non-)chronic drug was prescribed, indicating that this group was not completely healthy as well. The association between other psychological diagnoses and chronic somatic diseases might be explained by the inclusion of patients with anxiety (symptoms and disorders) in this group, since previous research found an association between somatic diseases and anxiety (20). Further research is needed to determine whether psychological distress in general is associated with higher rates of somatic disease, or whether specific psychological symptoms and disorders (e.g. anxiety and depression) are responsible.

**Strengths and limitations**

A major strength of our study was the large number of patients included. Furthermore, NIVEL-PCD consisted of routinely recorded data, reflecting everyday

practice. We also used data on dispensed rather than prescribed drugs, which more closely reflected actual use. Limitations are that we depended on correct coding by physicians, and could not exclude the possibility that patients with depressive symptoms were present in all groups. This is in fact supported by our observed prevalence of depression of 4.8%, which is substantially lower than the described prevalence of depression in primary care (1), indicating that some depressed patients have not been recognized and therefore misclassified as mentally healthy or misclassified as having another psychological diagnosis. However, the presence of depressed patients in the two comparison groups (false-negatives) would have led to an underestimation rather than overestimation of the associations. Furthermore, the cross-sectional design of our study limits inferences on causality. Not only is the direction of a possible causal relation unclear, it might well be that these concepts are just consequences of another causal factor, instead of the existence of a reciprocal causal relation. Also, the group with other psychological diagnoses is very heterogeneous, as can be seen in the Supplementary Data Table S2, which may have affected our results.

### Implications

General practitioners should be aware that late-life depression is associated with multimorbidity, polypharmacy, and the chronic use of anticholinergic and sedative drugs. This increases the vulnerability of these patients to adverse drug-related events. Critical drug reviews can reduce issues with polypharmacy in primary care (21). However, further research is needed to determine whether older depressed patients might specifically benefit as a group from such reviews, and whether adverse events can be prevented. Where possible, efforts should be made to treat late-life depression with psychological interventions rather than resorting to antidepressants in the first instance. Furthermore, our findings suggest that depressed primary care patients may be an important target for health promotion and other behavioral interventions to manage chronic disease instead of or in addition to pharmacological means. Finally, future research should specifically investigate the characteristics responsible for the association between differences in general practices and the rates of chronic somatic diseases and chronically used drugs.

## CONCLUSION

Late-life depression in primary care is associated with increased chronic use of drugs, even after excluding antidepressants and allowing for the higher rate of comorbid somatic diseases. Furthermore, these patients chronically use more non-antidepressant drugs with anticholinergic and sedative effects than their non-depressed peers. These findings indicate the need for regular medication reviews and for ensuring that alternative approaches are used for the treatment of late-life depression.

### Supplementary material

Supplementary material is available at *Family Practice* online.

### Declaration

Funding: Netherlands Organization for Health Research and Development (839110009). The funding provider had no involvement in the design, methods, analysis or preparation of this manuscript.

Ethical approval: According to the Institutional Review Board of the University Medical Center Groningen (UMCG), no approval was needed as this non-invasive study was not subject to the Dutch Medical Research Involving Human Subjects Act. The principal aim of this Act is to provide protection for human subjects who take part in medical research.
Conflict of interest: none.

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**REFERENCES**

1. Licht-Strunk E, van der Kooij KG, van Schaik DJ et al. Prevalence of depression in older patients consulting their general practitioner in The Netherlands. Int J Geriatr Psychiatry 2005; 20: 1013–9.
2. Caughey GE, Vitry AI, Gilbert AL, Roughead EE. Prevalence of comorbidity of chronic diseases in Australia. BMC Public Health 2008; 8: 221.
3. Gunn JM, Ayton DR, Densley K et al. The association between chronic illness, multimorbidity and depressive symptoms in an Australian primary care cohort. Soc Psychiatry Psychiatr Epidemiol 2012; 47: 175–84.
4. Calderon-Larranaga A, Gimeno-Feliu LA, Gonzalez-Rubio F et al. Polypharmacy patterns: unravelling systematic associations between prescribed medications. PLoS One 2013; 8: e84967.
5. Fried TR, O'Leary J, Towle V et al. Health outcomes associated with polypharmacy in community-dwelling older adults: a systematic review. J Am Geriatr Soc 2014; 62: 2261–72.
6. Antonelli Incalzi R, Corsonello A, Pedone C, Corica F, Carbonin P. Depression and drug utilization in an elderly population. Ther Clin Risk Manag 2005; 1: 55–60.
7. Verhaak PF, van Dijk CE, Nuijen J, Verheij RA, Schellevis FG. Mental health care as delivered by Dutch general practitioners between 2004 and 2008. Scand J Prim Health Care 2012; 30: 156–62.
8. Wouters H, van der Meer H, Taxis K. Quantification of anticholinergic and sedative drug load with the Drug Burden Index: a review of outcomes and methodological quality of studies. Eur J Clin Pharmacol 2017; 73: 257–66.
9. Verheij RA. Over NIVEL zorgregistraties; geschiedenis en achtergrond. www.nivel.nl/node/3464 (accessed on 24 November 2015).
10. Griens AMGF, Janssen JM, Kroon JDL et al. SFK Facts and Figures 2014. The Hague: Foundation for Pharmaceutical Statistics (SFK), 2014.
11. Hek K, Elffers B, Kroon JDL et al. Verantwoording koppeling huisartsen en apotheken. www.nivel.nl/node/3535 (accessed 24 November 2015).
12. Hoeymans N, van Oostrom SH, Gijsen R, Schellevis F. RIVM: Selectie van chronische ziekten. http://www.nationaalkompas.nl/gezondheid-en-ziekte/ziekten-en-aandoeningen/chronische-ziekten-en-multimorbiditeit/selectievan-chronische-ziekten/ (accessed 24 November 2015).
13. NHG. Multidisciplinaire richtlijn polyfarmacie bij ouderen, 2012. Utrecht: Nederlands Huisartsen Genootschap, 2012.
14. Hilmer SN, Mager DE, Simonsick EM et al. A drug burden index to define the functional burden of medications in older people. Arch Intern Med 2007; 167: 781–7.
15. van der Meer HG, Wouters H, van Hulten R, Pras N, Taxis K. Decreasing the load? Is a multidisciplinary multistep medication review in older people an effective intervention to reduce a patient's drug burden index? Protocol of a randomised controlled trial. BMJ Open 2015; 5: e009213.
16. Knol F, Boelhouwer J, Veldheer V. Statusontwikkeling van wijken in nederland 1998–2010. Den Haag: Sociaal en cultureel planbureau, 2012.

17. Privacybescherming NIVEL zorgregistraties. uit: NIVEL zorgregistraties eerste lijn. www.nivel.nl/node/3470 (accessed 24 November 2015).
18. Coutinho LM, Scazufca M, Menezes PR. Methods for estimating prevalence ratios in cross-sectional studies. Rev Saude Publica 2008; 42: 992–8.
19. Onder G, Liperoti R, Fialova D et al.; SHELTER Project. Polypharmacy in nursing home in Europe: results from the SHELTER study. J Gerontol A Biol Sci Med Sci 2012; 67: 698–704.
20. Chapman DP, Perry GS, Strine TW. The vital link between chronic disease and depressive disorders. Prev Chronic Dis 2005; 2: A14.
21. Fick DM, Maclean JR, Rodriguez NA et al. A randomized study to decrease the use of potentially inappropriate medications among community- dwelling older adults in a southeastern managed care organization. Am J Manag Care 2004; 10(11 Pt 1): 761–8.

## TABLES AND FIGURES

Table 1. Characteristics of the diagnostic groups ‘depressed’, ‘other psychological diagnoses’ and ‘mentally healthy controls’ as registered in general practice in 2012

| | **Depressed (*N* = 1512)** | **Psychological diagnoses (*N* = 1457)** | **Controls (*N* = 1508)** | ***P* value*** |
|---|---|---|---|---|
| Female | 1053 (69.6) | 1001 (68.7) | 1052 (69.8) | 0.792 |
| Age | 69.65 (7.69) | 69.76 (7.60) | 69.59 (7.61) | 0.771 |
| SES categories[a] | | | | 0.006 |
| Low | 345 (22.8) | 307 (21.1) | 362 (24.0) | |
| Medium | 872 (57.7) | 923 (63.3) | 899 (59.6) | |
| High | 295 (19.5) | 227 (15.6) | 247 (16.4) | |
| Chronic diseases | | | | |
| AIDS and HIV infection | 0 (0) | 1 (0.1) | 1 (0.1) | 0.600 |
| Malignancy | 284 (18.8) | 272 (18.7) | 242 (16.0) | 0.086 |
| Visual disorders | 204 (13.5) | 203 (13.9) | 184 (12.2) | 0.349 |

| | **Depressed (*N* = 1512)** | **Psychological diagnoses (*N* = 1457)** | **Controls (*N* = 1508)** | ***P* value*** |
|---|---|---|---|---|
| Hearing disorders | 163 (10.8) | 152 (10.4) | 130 (8.6) | 0.104 |
| Congenital cardiovascular anomaly | 3 (0.2) | 5 (0.3) | 2 (0.1) | 0.464 |
| Disorders of endocard/valvular heart disease | 38 (2.5) | 34 (2.3) | 37 (2.5) | 0.949 |
| Heart failure | 62 (4.1) | 51 (3.5) | 49 (3.2) | 0.437 |
| Coronary heart disease | 228 (15.1) | 213 (14.6) | 198 (13.1) | 0.279 |
| Arrhythmias | 98 (6.5) | 106 (7.3) | 90 (6.0) | 0.352 |
| Stroke | 129 (8.5) | 126 (8.6) | 104 (6.9) | 0.143 |
| Rheumatoid arthritis | 57 (3.8) | 38 (2.6) | 48 (3.2) | 0.198 |
| Peripheral arthritis | 353 (23.3) | 313 (21.5) | 317 (21.0) | 0.264 |
| Chronic neck and back pain | 177 (11.7)[3] | 139 (9.5) | 138 (9.2)[1] | 0.044[b] |
| Osteoporosis | 148 (9.8) | 142 (9.7) | 129 (8.6) | 0.420 |
| Parkinson’s disease | 28 (1.9)[2,3] | 7 (0.5)[1] | 8 (0.5)[1] | <.001 |
| Epilepsy | 19 (1.3) | 24 (1.6) | 14 (0.9) | 0.217 |
| Migraine | 31 (2.1) | 30 (2.1) | 17 (1.1) | 0.081 |
| COPD | 205 (13.6)[3] | 194 (13.3)[3] | 115 (7.6)[1,2] | <.001 |
| Asthma | 138 (9.1) | 121 (8.3) | 113 (7.5) | 0.267 |

| | **Depressed (*N* = 1512)** | **Psychological diagnoses (*N* = 1457)** | **Controls (*N* = 1508)** | ***P* value*** |
|---|---|---|---|---|
| Diabetes mellitus | 270 (17.9) | 276 (18.9) | 287 (19.0) | 0.654 |
| Number of chronic somatic diseases | 1.74 (1.46)[3] | 1.68 (1.44)[3] | 1.47 (1.33)[1,2] | <0.001 |
| Multimorbidity | 760 (50.3)[3] | 693 (47.6)[3] | 603 (40.0)[1,2] | <0.001 |
| Number of chronic medicines | 4.47 (3.01)[2,3] | 3.55 (2.78)[1,3] | 2.91 (2.34)[1,2] | <0.001 |
| Number of chronic medicines excl. antidepressants | 3.82 (2.96)[2,3] | 3.44 (2.76)[1,3] | 2.89 (2.32)[1,2] | <0.001 |
| Polypharmacy | 655 (43.3)[2,3] | 471 (32.3)[1,3] | 330 (21.9)[1,2] | <0.001 |
| Polypharmacy excl. antidepressants | 543 (35.9)[2,3] | 458 (31.4)[1,3] | 327 (21.7)[1,2] | <0.001 |
| Antidepressants chronically used | 996 (65.9)[2,3] | 167 (11.5)[1,3] | 34 (2.3)[1,2] | <0.001 |
| Drug Burden Index | 1.55 (1.29)[2,3] | 1.04 (1.06)[1,3] | 0.68 (0.79)[1,2] | <0.001 |
| Drug Burden Index excl. antidepressants | 1.11 (1.17)[2,3] | 0.96 (1.01)[1,3] | 0.67 (0.78)[1,2] | <0.001 |
| | Depressed (*N* = 1512) | Psychological diagnoses (*N* = 1457) | Controls (*N* = 1508) | *P* value* |
| Female | 1053 (69.6) | 1001 (68.7) | 1052 (69.8) | 0.792 |

| | **Depressed (*N* = 1512)** | **Psychological diagnoses (*N* = 1457)** | **Controls (*N* = 1508)** | ***P* value*** |
|---|---|---|---|---|
| Age | 69.65 (7.69) | 69.76 (7.60) | 69.59 (7.61) | 0.771 |
| SES categories[a] | | | | 0.006 |
| Low | 345 (22.8) | 307 (21.1) | 362 (24.0) | |
| Medium | 872 (57.7) | 923 (63.3) | 899 (59.6) | |
| High | 295 (19.5) | 227 (15.6) | 247 (16.4) | |
| Chronic diseases | | | | |
| AIDS and HIV infection | 0 (0) | 1 (0.1) | 1 (0.1) | 0.600 |
| Malignancy | 284 (18.8) | 272 (18.7) | 242 (16.0) | 0.086 |
| Visual disorders | 204 (13.5) | 203 (13.9) | 184 (12.2) | 0.349 |
| Hearing disorders | 163 (10.8) | 152 (10.4) | 130 (8.6) | 0.104 |
| Congenital cardiovascular anomaly | 3 (0.2) | 5 (0.3) | 2 (0.1) | 0.464 |
| Disorders of endocard/valvular heart disease | 38 (2.5) | 34 (2.3) | 37 (2.5) | 0.949 |
| Heart failure | 62 (4.1) | 51 (3.5) | 49 (3.2) | 0.437 |
| Coronary heart disease | 228 (15.1) | 213 (14.6) | 198 (13.1) | 0.279 |
| Arrhythmias | 98 (6.5) | 106 (7.3) | 90 (6.0) | 0.352 |

| | **Depressed (*N* = 1512)** | **Psychological diagnoses (*N* = 1457)** | **Controls (*N* = 1508)** | ***P* value*** |
|---|---|---|---|---|
| Stroke | 129 (8.5) | 126 (8.6) | 104 (6.9) | 0.143 |
| Rheumatoid arthritis | 57 (3.8) | 38 (2.6) | 48 (3.2) | 0.198 |
| Peripheral arthritis | 353 (23.3) | 313 (21.5) | 317 (21.0) | 0.264 |
| Chronic neck and back pain | 177 (11.7)[3] | 139 (9.5) | 138 (9.2)[1] | 0.044[b] |
| Osteoporosis | 148 (9.8) | 142 (9.7) | 129 (8.6) | 0.420 |
| Parkinson's disease | 28 (1.9)[2,3] | 7 (0.5)[1] | 8 (0.5)[1] | <.001 |
| Epilepsy | 19 (1.3) | 24 (1.6) | 14 (0.9) | 0.217 |
| Migraine | 31 (2.1) | 30 (2.1) | 17 (1.1) | 0.081 |
| COPD | 205 (13.6)[3] | 194 (13.3)[3] | 115 (7.6)[1,2] | <.001 |
| Asthma | 138 (9.1) | 121 (8.3) | 113 (7.5) | 0.267 |
| Diabetes mellitus | 270 (17.9) | 276 (18.9) | 287 (19.0) | 0.654 |
| Number of chronic somatic diseases | 1.74 (1.46)[3] | 1.68 (1.44)[3] | 1.47 (1.33)[1,2] | <0.001 |
| Multimorbidity | 760 (50.3)[3] | 693 (47.6)[3] | 603 (40.0)[1,2] | <0.001 |
| Number of chronic medicines | 4.47 (3.01)[2,3] | 3.55 (2.78)[1,3] | 2.91 (2.34)[1,2] | <0.001 |
| Number of chronic medicines excl. antidepressants | 3.82 (2.96)[2,3] | 3.44 (2.76)[1,3] | 2.89 (2.32)[1,2] | <0.001 |

| | **Depressed (*N* = 1512)** | **Psychological diagnoses (*N* = 1457)** | **Controls (*N* = 1508)** | ***P* value*** |
|---|---|---|---|---|
| Polypharmacy | 655 (43.3)[2,3] | 471 (32.3)[1,3] | 330 (21.9)[1,2] | <0.001 |
| Polypharmacy excl. antidepressants | 543 (35.9)[2,3] | 458 (31.4)[1,3] | 327 (21.7)[1,2] | <0.001 |
| Antidepressants chronically used | 996 (65.9)[2,3] | 167 (11.5)[1,3] | 34 (2.3)[1,2] | <0.001 |
| Drug Burden Index | 1.55 (1.29)[2,3] | 1.04 (1.06)[1,3] | 0.68 (0.79)[1,2] | <0.001 |
| Drug Burden Index excl. antidepressants | 1.11 (1.17)[2,3] | 0.96 (1.01)[1,3] | 0.67 (0.78)[1,2] | <0.001 |

Values are means (SD) or numbers (%).
[a]Similar to previous studies[16] SES was divided into quintiles. Highest or lowest quintiles were categorized as high or low SE score, respectively. Middle three quintiles categorized as medium SES score.
[b]No significant difference after Bonferroni correction.
*Using Chi square tests for categorical data (*N* (%)) and Kruskal Wallis tests for continuous data (mean (SD)). Using a Mann–Whitney *U* test as a post hoc analysis for Kruskal Wallis. Numbers in superscript refer to significant difference with respectively column 1 (depressed), column 2 (psychological diagnoses) and column 3 (controls).

Table 2. Association between diagnostic group and chronic diseases

| **Fixed effects** | **Number of chronic diseases[a]** | | | **Multimorbidity[b]** | | |
|---|---|---|---|---|---|---|
| | **PR** | **95% CI** | ***P* value** | **OR** | **95% CI** | ***P* value** |
| *Controls* | *Reference* | | *Reference* | | | |
| Depression[c] | 1.16 | 1.10–1.24 | <0.001 | 1.55 | 1.33–1.81 | <0.001 |

| Fixed effects | Number of chronic diseases[a] | | | Multimorbidity[b] | | |
|---|---|---|---|---|---|---|
| | **PR** | **95% CI** | ***P* value** | **OR** | **95% CI** | ***P* value** |
| Psychological diagnoses[c] | 1.12 | 1.05–1.18 | <0.001 | 1.34 | 1.15–1.57 | <0.001 |
| Age | | | | | | |
| 60–64 years | Reference | | | | | |
| 65–69 years | 1.22 | 1.14–1.31 | <0.001 | 1.36 | 1.15–1.61 | <0.001 |
| 70–74 years | 1.49 | 1.39–1.61 | <0.001 | 2.22 | 1.85–2.67 | <0.001 |
| 75–79 years | 1.65 | 1.53–1.79 | <0.001 | 3.12 | 2.55–3.83 | <0.001 |
| 80–84 years | 2.01 | 1.84–2.18 | <0.001 | 4.58 | 3.56–5.89 | <0.001 |
| ≥85 years | 2.02 | 1.82–2.25 | <0.001 | 4.43 | 3.21–6.10 | <0.001 |
| Female | 0.99 | 0.94–1.05 | 0.82 | 0.95 | 0.83–1.08 | 0.42 |
| SES | 0.99 | 0.99–1.00 | 0.003 | 0.99 | 0.97–1.00 | 0.06 |
| Random effects | Practice variation | 95% CI | *P*-value multilevel model | Practice variation | 95% CI | *P*-value multilevel model |
| General practice | 0.02 | 0.01–0.04 | <0.001 | 0.10 | 0.05–0.19 | <0.001 |

| Fixed effects | Number of chronic diseases[a] | | | Multimorbidity[b] | | |
|---|---|---|---|---|---|---|
| | PR | 95% CI | *P* value | OR | 95% CI | *P* value |
| Controls | Reference | | | Reference | | |
| Depression[c] | 1.16 | 1.10–1.24 | <0.001 | 1.55 | 1.33–1.81 | <0.001 |
| Psychological diagnoses[c] | 1.12 | 1.05–1.18 | <0.001 | 1.34 | 1.15–1.57 | <0.001 |
| Age | | | | | | |
| 60–64 years | Reference | | | | | |
| 65–69 years | 1.22 | 1.14–1.31 | <0.001 | 1.36 | 1.15–1.61 | <0.001 |
| 70–74 years | 1.49 | 1.39–1.61 | <0.001 | 2.22 | 1.85–2.67 | <0.001 |
| 75–79 years | 1.65 | 1.53–1.79 | <0.001 | 3.12 | 2.55–3.83 | <0.001 |
| 80–84 years | 2.01 | 1.84–2.18 | <0.001 | 4.58 | 3.56–5.89 | <0.001 |
| ≥85 years | 2.02 | 1.82–2.25 | <0.001 | 4.43 | 3.21–6.10 | <0.001 |
| Female | 0.99 | 0.94–1.05 | 0.82 | 0.95 | 0.83–1.08 | 0.42 |
| SES | 0.99 | 0.99–1.00 | 0.003 | 0.99 | 0.97–1.00 | 0.06 |
| Random effects | Practice variation | 95% CI | *P*-value multilevel | Practice variation | 95% CI | *P*-value multilevel |

| Fixed effects | Number of chronic diseases[a] | | | Multimorbidity[b] | | |
|---|---|---|---|---|---|---|
| | PR | 95% CI | *P* value | OR | 95% CI | *P* value |
| | | | model | | | model |
| General practice | 0.02 | 0.01–0.04 | <0.001 | 0.10 | 0.05–0.19 | <0.001 |

PR, Prevalence Ratio; 95% CI, 95% confidence interval; OR, odds ratio.
[a]Using multivariate multilevel negative binomial regression analysis with number of chronic diseases as dependent variable, adjusted for age, gender, SES and general practice.
[b]Using multivariate multilevel logistic regression analysis with multimorbidity (yes/no) as dependent variable, adjusted for age, gender, SES and general practice.
[c]No significant difference for both outcomes between depressed patients and patients with other psychological diagnoses (PR 1.04, *P* = 0.14; OR 1.16, *P* = 0.06).

Table 3. Association between diagnostic group and drugs, including antidepressants

| Fixed effects | Number of chronic drugs[a] | | | Polypharmacy[b] | | | Drug burden index[c] | | |
|---|---|---|---|---|---|---|---|---|---|
| | PR | 95% CI | *P*-value | OR | 95% CI | *P*-value | Coefficient | 95% CI | *P*-value |
| Controls | Reference | | | Reference | | | Reference | | |
| Depression[d] | 1.46 | 1.39 – 1.53 | <0.001 | 2.89 | 2.41 – 3.47 | <0.001 | 0.87 | 0.80 to 0.95 | <0.001 |
| Psychological diagnoses[‡] | 1.16 | 1.10 – 1.22 | <0.001 | 1.66 | 1.38 – 2.00 | <0.001 | 0.32 | 0.25 to 0.39 | <0.001 |
| Age | | | | | | | | | |
| 60–64 years | Reference | | | Reference | | | Reference | | |
| 65–69 years | 1.10 | 1.04 – 1.16 | <0.001 | 1.24 | 1.02 – 1.52 | 0.03 | 0.07 | −0.01 to 0.15 | 0.07 |

| Fixed effects | Number of chronic drugs[a] | | | Polypharmacy[b] | | | Drug burden index[c] | | |
|---|---|---|---|---|---|---|---|---|---|
| | **PR** | **95% CI** | ***P*-value** | **OR** | **95% CI** | ***P*-value** | **Coefficient** | **95% CI** | ***P*-value** |
| 70–74 years | 1.14 | 1.08 – 1.21 | <0.001 | 1.33 | 1.07 – 1.66 | 0.01 | 0.02 | −0.06 to 0.11 | 0.59 |
| 75–79 years | 1.22 | 1.14 – 1.30 | <0.001 | 1.72 | 1.36 – 2.18 | <0.001 | 0.15 | 0.05 to 0.25 | 0.003 |
| 80–84 years | 1.28 | 1.19 – 1.37 | <0.001 | 1.82 | 1.38 – 2.40 | <0.001 | 0.16 | 0.05 to 0.29 | 0.01 |
| ≥85 years | 1.26 | 1.15 – 1.38 | <0.001 | 2.00 | 1.40 – 2.84 | <0.001 | 0.10 | −0.05 to 0.25 | 0.18 |
| Female | 0.96 | 0.92 – 1.00 | 0.03 | 0.86 | 0.74 – 1.01 | .07 | 0.07 | −0.01 to 0.13 | 0.03 |
| Number of chronic diseases | 1.25 | 1.24 – 1.27 | <0.001 | 2.06 | 1.93 – 2.19 | <0.001 | 0.22 | 0.19 to 0.24 | <0.001 |
| SES | 1.00 | 0.99 – 1.00 | 0.06 | 0.99 | 0.97 – 1.00 | 0.11 | −0.01 | −0.01 to 0.00 | 0.08 |
| Random effects | Practice variation | 95% CI | *P*-value multilevel model | Practice variation | 95% CI | *P*-value multilevel model | Practice variation | 95% CI | *P*-value multilevel model |
| General practice | 0.01 | 0.01 – 0.02 | <0.001 | 0.15 | 0.08 – 0.29 | <0.001 | 0.05 | 0.04 – 0.08 | <0.001 |
| **Fixed effects** | **Number of chronic drugs[a]** | | | **Polypharmacy[b]** | | | **Drug burden index[c]** | | |
| | **PR** | **95% CI** | ***P*-value** | **OR** | **95% CI** | ***P*-value** | **Coefficient** | **95% CI** | ***P*-value** |
| Controls | Reference | | | Reference | | | Reference | | |

| Fixed effects | Number of chronic drugs[a] | | | Polypharmacy[b] | | | Drug burden index[c] | | |
|---|---|---|---|---|---|---|---|---|---|
| | PR | 95% CI | *P*-value | OR | 95% CI | *P*-value | Coefficient | 95% CI | *P*-value |
| Depression[d] | 1.46 | 1.39 – 1.53 | <0.001 | 2.89 | 2.41 – 3.47 | <0.001 | 0.87 | 0.80 to 0.95 | <0.001 |
| Psychological diagnoses[‡] | 1.16 | 1.10 – 1.22 | <0.001 | 1.66 | 1.38 – 2.00 | <0.001 | 0.32 | 0.25 to 0.39 | <0.001 |
| Age | | | | | | | | | |
| 60–64 years | Reference | | | Reference | | | Reference | | |
| 65–69 years | 1.10 | 1.04 – 1.16 | <0.001 | 1.24 | 1.02 – 1.52 | 0.03 | 0.07 | −0.01 to 0.15 | 0.07 |
| 70–74 years | 1.14 | 1.08 – 1.21 | <0.001 | 1.33 | 1.07 – 1.66 | 0.01 | 0.02 | −0.06 to 0.11 | 0.59 |
| 75–79 years | 1.22 | 1.14 – 1.30 | <0.001 | 1.72 | 1.36 – 2.18 | <0.001 | 0.15 | 0.05 to 0.25 | 0.003 |
| 80–84 years | 1.28 | 1.19 – 1.37 | <0.001 | 1.82 | 1.38 – 2.40 | <0.001 | 0.16 | 0.05 to 0.29 | 0.01 |
| ≥85 years | 1.26 | 1.15 – 1.38 | <0.001 | 2.00 | 1.40 – 2.84 | <0.001 | 0.10 | −0.05 to 0.25 | 0.18 |
| Female | 0.96 | 0.92 – 1.00 | 0.03 | 0.86 | 0.74 – 1.01 | .07 | 0.07 | −0.01 to 0.13 | 0.03 |
| Number of chronic diseases | 1.25 | 1.24 – 1.27 | <0.001 | 2.06 | 1.93 – 2.19 | <0.001 | 0.22 | 0.19 to 0.24 | <0.001 |
| SES | 1.00 | 0.99 | 0.06 | 0.99 | 0.97 | 0.11 | −0.01 | −0.0 | 0.08 |

| Fixed effects | Number of chronic drugs[a] | | | Polypharmacy[b] | | | Drug burden index[c] | | |
|---|---|---|---|---|---|---|---|---|---|
| | **PR** | **95% CI** | ***P*-value** | **OR** | **95% CI** | ***P*-value** | **Coefficient** | **95% CI** | ***P*-value** |
| | | – 1.00 | | | – 1.00 | | | 1 to 0.00 | |
| Random effects | Practice variation | 95% CI | *P*-value multilevel model | Practice variation | 95% CI | *P*-value multilevel model | Practice variation | 95% CI | *P*-value multilevel model |
| General practice | 0.01 | 0.01 – 0.02 | <0.001 | 0.15 | 0.08 – 0.29 | <0.001 | 0.05 | 0.04 – 0.08 | <0.001 |

PR, Prevalence Ratio; 95% CI, 95% confidence interval; OR, odds ratio.
[a]Using multivariate multilevel negative binomial regression analysis with number of chronically used drugs including antidepressants as dependent variable, adjusted for age, gender, SES, number of chronic diseases and general practice.
[b]Using multivariate multilevel logistic regression analysis with polypharmacy (yes/no) including antidepressants as dependent variable, adjusted for age, gender, SES, number of chronic diseases and general practice.
[c]Using multivariable multilevel linear regression analysis with Drug Burden Index including antidepressants as dependent variable, adjusted for age, gender, SES, number of chronic diseases, and general practice.
[d]Significant difference for all outcomes between depressed patients and patients with other psychological diagnoses (PR 1.26, $P < 0.001$; OR 1.75, $P < 0.001$; coefficient .56, $P < 0.001$).