

Original Article

Polypharmacy Among 200 000 Subjects of the Population-Based German National Cohort Study (NAKO), Aged 19–74

A Baseline Analysis

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Summary

Background: Polypharmacy is associated with adverse events, reduced quality of life, and increased mortality, but population-based studies including both prescribed and over-the-counter medications are scarce.

Methods: We analyzed baseline data from the German National Cohort (NAKO), Germany's largest population-based cohort study (recruitment 2014–2019; participants aged 19–74 years at baseline). We estimated the proportion of participants with polypharmacy (defined as reporting regular use of ≥ 5 prescribed and over-the-counter medications) and hyperpolypharmacy (≥ 10 medications), stratified by sex and age. Determinants of polypharmacy were estimated using logistic regression.

Results: Among 203 765 participants (mean age 49.8 years, 50.4% female), 6869 women (6.7%; 95% confidence interval [6.5; 6.8]) and 8126 men (8.0% [7.9; 8.2]) reported regular use of ≥ 5 medications. Regular use of ≥ 10 medications was reported by 505 women (0.5% [0.45; 0.54]) and 722 men (0.7% [0.67; 0.77]). Polypharmacy and hyperpolypharmacy increased with age. Diabetes and chronic cardiovascular conditions were strong determinants. Use of cardiovascular medications was most frequently reported.

Conclusion: Polypharmacy was common in NAKO, particularly among older participants, men, and persons with cardiovascular disease. Because medication appropriateness could not be assessed, future studies should examine inappropriate polypharmacy and evaluate risk factors and strategies for deprescribing.

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Polypharmacy, typically defined as the concurrent use of multiple medications by a single patient, has been associated with a range of unfavourable health outcomes, including:

- Falls
- Cognitive impairment
- Functional decline
- Hospitalization
- Mortality (1, 2)

Concomitant intake of five or more drugs is commonly used as a cut-off to define polypharmacy; however, some studies only include prescribed medicines, while others also include over-the-counter (OTC) medications (3).

A recent meta-analysis of 54 observational studies estimated a pooled prevalence of polypharmacy of 37% (4). In Germany, polypharmacy is additionally fostered by the fragmented German healthcare system, and several studies have reported prevalences of polypharmacy

in older adults between 27% and 90% (5–13). Studies without restrict of their population to older adults have reported figures between 4% and 20% (14–16). An analysis using German routine claims data found that 14% of about 1.3 million insured persons had multimorbidity—defined as presence of three or more chronic diseases—combined with polypharmacy (17). However, almost all studies conducted in Germany have limitations. Given the strong association between polypharmacy and adverse outcomes in older adults, many studies to date have focused predominantly on this age group, often excluding young adults and the middle-aged. Additional limitations include restricted study areas, i.e., including only residents of certain cities

or federal states, small sample sizes, or lack of information on OTC drug purchases.

Against this backdrop, the present analysis aims to provide estimates regarding the proportion of persons with polypharmacy in Germany, using data that contain information on prescribed and OTC medications. Moreover, determinants of polypharmacy were assessed using disease-related and lifestyle variables.

Method

This study utilizes data from the NAKO Health Study, Germany's largest cohort study. The primary aim of NAKO is to investigate the etiology of major chronic diseases, their preclinical stages, and functional health impairments. During baseline recruitment (2014–2019) data from 205 053 adults of the general German population aged 20–69 years were collected at 18 study centers in 13 federal states. The upper age limit at recruitment was 69 years. As the baseline examinations were conducted over several years, some participants had reached or exceeded the age of 70 years by the time of their baseline assessment. The probands were randomly sampled from local population registries in the catchment areas of the participating study centers. Because incidence of most chronic diseases peaks in older age, persons aged ≥ 40 years were intentionally oversampled during recruitment. The response rate was 15.6% overall and varied between 7.6% and 30.7% across study centers (18).

Assessment of medication use

Medication intake was assessed by computer-assisted face-to-face interviews. Participants were asked to bring packages of all medications they had used in the previous 7 days. Based on the pharmaceutical identification number (PZN) and a database-supported identification system, detailed information e.g., Anatomical Therapeutic Chemical (ATC) code and strength, was recorded for each medication. In the interview, the following information was collected for each medication:

- Number of tablets per day
- Duration of use
- Frequency of use (regularly or as needed)
- Prescription by a physician (yes or no)

If participants forgot to bring their packages, the medication was selected manually from the database-supported identification system. If selection from the identification system was not possible, the medication was recorded in free text. Information in free-text fields was coded manually based on the ATC classification system, where applicable. Dietary supplements and other active ingredients without an ATC code were coded manually using a classification created specifically for these substance groups.

In line with previous studies (3), polypharmacy was defined as reported intake of at least five prescribed or OTC medications at baseline. Additionally, we looked at hyperpolypharmacy—defined as a special case of polypharmacy with intake of ten or more medications—at baseline (3, 19, 20). As in previous nationwide analyses of polypharmacy in Germany, dietary supplements, homeopathic or anthroposophical drugs, and non-systemically acting drugs such as creams and eyedrops were excluded from the definition of polypharmacy and hyperpolypharmacy (13, 16). A list of the excluded ATC codes can be found in *eSupplement-Table S1*.

We performed a descriptive analysis to estimate the proportions of study participants with polypharmacy and hyperpolypharmacy. Both analyses were stratified by sex and age. Only medications taken regularly were included in the main analysis. The analysis was then repeated using all medications—taken regularly or as needed. Wilson's method was used to estimate 95% confidence intervals (95% CI) (21).

The proportions of men and women who used medications from particular drug classes were calculated to establish medication use. After exclusion of participants with incomplete ATC codes—no second-level ATC codes or missing values for ATC codes ($n = 585$)—or missing data on frequency of use ($n = 530$), 203 765 persons were included for analysis. Logistic regression models were used to identify determinants of polypharmacy. A detailed description of the modeling process can be found in the *eSupplement-Methods*.

Data preprocessing and all analyses were performed using R version 4.3.3 (R Core Team 2023), employing the packages dplyr (version 1.1.4) (22), data.table (version 1.15.2) (23), and rms (version 7.0–0) (24).

Results

The baseline characteristics of all 203 765 NAKO participants included in the analysis are presented in *Table 1* and in *eSupplement-Table S2* of the *eSupplement-Methods*. The participants' mean age was 60.5 years for those with polypharmacy and 61.4 years for those with hyperpolypharmacy. Compared to the total study population, the frequencies of all assessed comorbidities were higher in the polypharmacy and hyperpolypharmacy subsamples. Altogether, 59.6% of participants with polypharmacy and 34.0% of those with hyperpolypharmacy rated their overall health status as good or better.

The proportions of study participants with polypharmacy and hyperpolypharmacy in the total study population, stratified by sex and age group, are shown in *Table 2*. Taking only regularly used medications into account, 14 995 (7.4%, 95% CI [7.2; 7.5]) of the 203 765 participants were exposed to polypharmacy and 1227 (0.6% [0.57; 0.64]) to hyperpolypharmacy. Polypharmacy was reported by 6869 of the 102 733 female probands (6.7% [6.5; 6.8]) and by 8126 of the 101 032 male probands (8.0% [7.9; 8.2]). The proportion of persons with polypharmacy increased with age: 8465 (16.8% [16.4; 17.1]) of the 50 526 participants aged 60–69 years and 1066 (24.5% [23.2; 25.8]) of the 4355 participants aged 70–74 years were exposed to polypharmacy. Hyperpolypharmacy was present in 505 (0.5% [0.45; 0.54]) female and 722 (0.7% [0.67; 0.77]) male participants. While hyperpolypharmacy was present in hardly any probands younger than 50 years, it was observed much more often in those aged 60 years and older.

Extension to all reported medications, including medications used as needed, increased the proportions of participants with polypharmacy to 11.0% [(10.8; 11.2] of women and 10.2% [10.0; 10.4] of men (*eSupplement-Table S3*).

The *Figure* shows the top ten drug classes used by men and women with polypharmacy and hyperpolypharmacy. Among these ten most frequent used classes of drugs, nine were consistent between males and females with polypharmacy and hyperpolypharmacy. Substances for the treatment of cardiovascular diseases (ATC classes C and B01) were the most prominent medications.

The determinants of polypharmacy are listed in *eSupplement-Table S4* and discussed in the *eSupplement-Results*. In brief, females had higher odds of polypharmacy than males after adjustment for age and comorbidity burden. The probability of reporting

polypharmacy increased gradually up to the age of 40 years and more sharply thereafter. Previous self-reported diagnoses of myocardial infarction, diabetes and arterial hypertension, epilepsy, and the presence of depression were also identified as predictors of polypharmacy.

Discussion

This study assessed the frequency and determinants of polypharmacy in a population-based sample from Germany. Polypharmacy was present in 6869 (7.4%) of the female and 8126 (8.0%) of the male participants, and hyperpolypharmacy was identified in 505 women (0.5%) and 722 men (0.7%). These proportions are lower than those published in previous studies that used samples of the general German population. A cross-sectional analysis of the Rhineland study, which included persons aged between 30 and 95 years, reported the presence of polypharmacy—defined as any use of prescribed and OTC medications—in 15.9% of the first 5000 participants (14). An analysis of the first wave of the German DEGS study, which included adults aged 18–79 years, found polypharmacy (defined as in the the Rhineland study) in 18.3% of the study population (15). An analysis based on data from the EPIC Heidelberg cohort reported prevalences of polypharmacy—defined as regular intake of prescribed and OTC medications—of 3.5% and 11.9%. These figures also resemble our findings (16). Differences in reported polypharmacy prevalence across studies largely reflect methodological heterogeneity, including differences:

- In study populations (e.g., many more highly educated and healthy participants in NAKO)
- In the definitions of polypharmacy
- Regarding the medications included in the analyses (e.g., all medications or only those taken regularly, time window used to assess medication exposure)
- In the data sources used to assess medication exposure

Our findings regarding age and sex differences in medication use are consistent with the results of an analysis of prescribed medications based on routine data from a German health insurance fund, the *Techniker Krankenkasse* (25). In that analysis, the volume of prescribed medications increased with age. In addition, the report found sex differences resembling our findings: for example, men had particularly high prescription volumes for cardiovascular medications. In line with previous studies, we identified agents acting on the renin–angiotensin system, beta-blockers, and lipid-lowering agents as drug classes commonly used by male and female participants with polypharmacy (10, 14, 26). This is plausible given the therapeutic overlap of these medications. Notably, several of the drug classes most frequently used in our analysis—particularly lipid-lowering agents and antihypertensives—are among those commonly targeted in deprescribing initiatives. Such initiatives aim to reduce the medication burden and potentially inappropriate prescribing in older or multimorbid patients. Evidence from structured deprescribing interventions indicates that medication reviews focusing on these drug classes can reduce the treatment burden in selected groups of patients (27, 28). This suggests that the NAKO population

Table 1

Characteristics of the 203 765 NAKO participants included in the analysis, stratified by polypharmacy status*¹

	Overall	Polypharmacy (≥ 5 medications)	Hyperpolypharmacy (≥ 10 medications)
n ²	203 765 (100)	14 995 (7.4)	1227 (0.6)
Age* ³	49.8 (12.8)	60.5 (8.1)	61.4 (7.3)
Female* ²	102 733 (50.4)	6869 (45.8)	505 (41.2)
Income*²			
< 60% of MNEI	28 213 (14.9)	0	397 (34.3)
60–< 80% of MNEI	27 357 (14.4)	2898 (20.7)	256 (22.1)
80–< 100% of MNEI	27 174 (14.3)	1951 (13.9)	138 (11.9)
100–< 150% of MNEI	58 828 (31.0)	3612 (25.8)	242 (20.9)
≥ 150 % of MNEI	48 321 (25.4)	2297 (16.4)	126 (10.9)
Level of education*²			
Low	5161 (2.7)	775 (5.6)	83 (7.5)
Medium	77 971 (41.2)	6920 (50.4)	582 (52.8)
High	102 013 (53.9)	6005 (43.8)	437 (39.6)
No qualification	4269 (2.3)	19 (0.1)	1 (0.1)
Self-rated state of health*^{2,4}			
Excellent	7282 (3.7)	77 (0.6)	6 (0.5)
Very good	57 988 (29.6)	677 (4.9)	20 (1.8)
Good	108 264 (55.3)	7533 (54.1)	347 (31.7)
Less good	20 356 (10.4)	4935 (35.4)	565 (51.6)
Poor	1798 (0.9)	706 (5.1)	156 (14.3)
Alcohol consumption*⁵			
Hazardous consumption	68 956 (35.5)	4001 (29.3)	213 (20.0)
Smoking*²			
Never	90 120 (46.2)	4632 (33.6)	332 (30.9)
Former	40 019 (20.5)	2697 (19.6)	213 (19.8)
Current	65 010 (33.3)	6447 (46.8)	531 (49.3)
Body mass index*²			
Underweight	2131 (1.1)	46 (0.3)	2 (0.2)
Normal weight	80 230 (40.5)	2133 (14.9)	103 (9.0)
Overweight	73 110 (36.9)	4826 (33.8)	281 (24.6)
Obese	42 682 (21.5)	7290 (51.0)	755 (66.2)

An exhaustive description of the variables and a more detailed version of this Table including the presence of comorbidities can be found in eSupplement-Methods and eSupplement-Table S2.

*¹ Definitions of polypharmacy and hyperpolypharmacy and a description of documentation techniques can be found in eSupplement-Methods.

*² Expressed as n (%)

*³ Expressed as mean (with standard deviation). The upper age limit at the time of recruitment was 69 years. Because the baseline surveys took place over a period of 5 years, some participants were ≥ 70 years old by the time their baseline data were acquired.

*⁴ Documented by means of the WHOQOL-BREF questionnaire

*⁵ Documented by means of the AUDIT-C-Score questionnaire
MNEI, Monthly net equivalent income; n, sample size

Table 2

Proportions of participants with polypharmacy and hyperpolypharmacy in the total study population and stratified by sex and age group

	Total	Polypharmacy (≥ 5 medications)			Hyperpolypharmacy (≥ 10 medications)		
		Share (n)	Proportion (%)	[95% CI]	Share (n)	Proportion (%)	[95% CI]
All participants	203 765	14 995	7.4	[7.2; 7.5]	1227	0.60	[0.57; 0.64]
Women	102 733	6869	6.7	[6.5; 6.8]	505	0.49	[0.45; 0.54]
Men	101 032	8126	8.0	[7.9; 8.2]	722	0.72	[0.67; 0.77]
Age group*2							
18–29 years	19 907	80	0.4	[0.3; 0.5]	3	0.02	[0.01; 0.04]
30–39 years	21 550	203	0.9	[0.8; 1.1]	6	0.03	[0.01; 0.06]
40–49 years	52 755	1305	2.5	[2.3; 2.6]	80	0.15	[0.12; 0.19]
50–59 years	54 672	3876	7.1	[6.9; 7.3]	307	0.56	[0.50; 0.63]
60–69 years	50 526	8465	16.8	[16.4; 17.1]	734	1.45	[1.35; 1.56]
70–74 years	4355	1066	24.5	[23.2; 25.8]	97	2.23	[1.83; 2.71]

*1 Definitions of polypharmacy and hyperpolypharmacy and a description of data assessment can be found in *eSupplement-Methods*. For the sake of accuracy, the figures for hyperpolypharmacy are given to two decimal places. A list of the medications not counted towards polypharmacy can also be found in *eSupplement-Methods*.

*2 The upper age limit for recruitment was 69 years. Because the baseline surveys were conducted over a period of 5 years, some participants were aged 70 years or over by the time they were interviewed.

CI, Confidence interval; n, number of participants

includes a substantial proportion of persons for whom structured medication reviews and deprescribing or medication optimization could be clinically relevant.

Strengths and limitations

Our analysis provides a comprehensive description of polypharmacy and hyperpolypharmacy in the NAKO study. While previous studies focused on certain age groups, e.g., older adults, or recruited in specific regions of Germany, we analyzed the entire population aged 19–74 years, stratified by age and sex. Further strengths of our analysis include the large sample size and the detailed assessment of medication use. A major strength of NAKO is the use of computer-assisted face-to-face interviews, where participants were asked to bring medication packages used in the previous 7 days. This helped minimize potential recall bias and missing data on medication intake.

However, our results are not generalizable to the German population due to the low response rates—especially among younger persons (29)—the uneven distribution of the NAKO study centers across Germany—which led to underrepresentation of rural areas—and the presence of healthy volunteer bias. Polypharmacy was assessed within the age range covered by the NAKO cohort, and the absence of participants aged ≥ 75 years should therefore be considered when interpreting the reported prevalences. This is particularly relevant, as the prevalence of polypharmacy increases with advancing age. Our oversampling of older age groups within the NAKO survey could partially mitigate this limitation, but it does not compensate for the absence of the oldest age groups. Overall, these limitations cause our estimates of polypharmacy to be

biased downwards and to underestimate the overall prevalence in the German population.

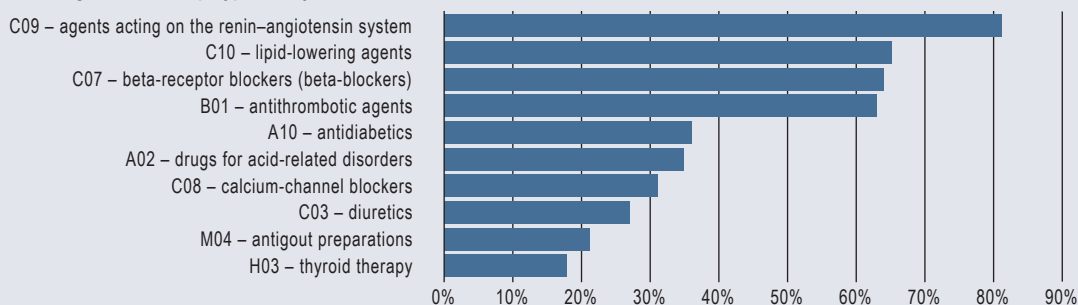
Although the assessment of medication use within the previous 7 days allowed for precise monitoring of regularly used medications, drugs taken at longer regular intervals (e.g., monthly) may have been underreported. Furthermore, comorbidities were assessed via self-report in a standardized interview, which may lead to some degree of misclassification if participants are unaware of or inaccurately recall their diagnoses. Lastly, we could not determine whether polypharmacy was inappropriate or a result of prescribing according to guidelines, as that information is not included in the data. This is an area of future research in NAKO. However, focusing on adults below 75 years of age provides important insights into polypharmacy in midlife and early old age, when preventive strategies and optimization of medication may be particularly effective in minimizing progression to polypharmacy and medication-related adverse events in later life.

Conclusions

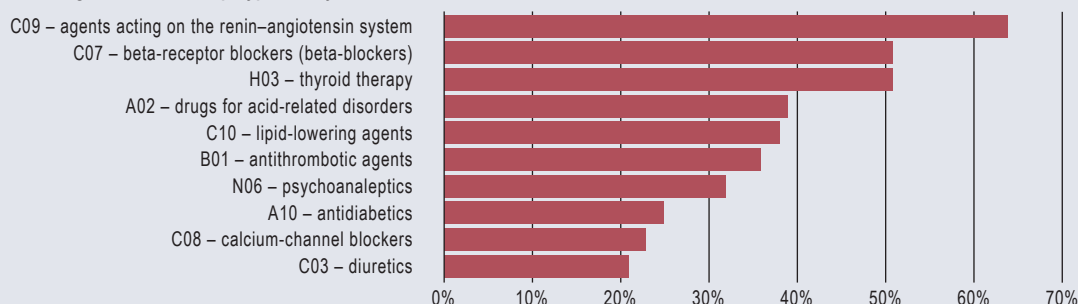
Our findings show that polypharmacy was relatively common. Polypharmacy increased with age and was slightly more common in men than in women. While a particular strength of this study lies in the assessment of actual medication intake during the previous 7 days—including OTC medications available in the NAKO cohort—our findings did not allow us to assess the appropriateness of the polypharmacy. In this context, medication optimization should be considered a key strategy to improve drug safety, particularly in populations with a high medication burden. Future studies should therefore focus on assessing medication appropriateness and identifying predictors of

Figure

Classes of drugs in men with polypharmacy



Classes of drugs in women with polypharmacy



The ten most frequently used classes of drugs in men and women with polypharmacy (at least five medications taken regularly). The figure shows the proportion of participants regularly taking at least one drug from the ATC class concerned. More than one response could be given.

inappropriate polypharmacy. Furthermore, upcoming developments, such as the nationwide introduction of electronic patient records in Germany, should be considered, as they may influence the frequency and patterns of polypharmacy.

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Conflict of interest statement

André Karch ist President of the German Society for Epidemiology.

Tobias Pischon is a NAKO e.V. committee member.

The remaining authors declare that no conflict of interest exists.

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References (abbreviated)

1. Chang TI, et al.: *Sci Rep* 2020; 10: 18964.
2. Sheppard JP, et al.: *Lancet Healthy Longev* 2024; 5: e563–73.
3. Masnoon N, et al.: *BMC Geriatr* 2017; 17: 230.
4. Delara M, et al.: *BMC Geriatr* 2022; 22: 601.

5. Bennie M, et al.: *Br J Clin Pharmacol* 2024; 90: 2124–36.
6. Dörks M, et al.: *Drugs Aging* 2016; 33: 45–51.
7. Junius-Walker U, et al.: *Fam Pract* 2007; 24: 14–9.
8. Kostev K, et al.: *J Psychiatr Res* 2023; 157: 192–6.
9. Midão L, et al.: *Arch Gerontol Geriatr* 2018; 78: 213–20.
10. Mielke N, et al.: *BMC Geriatr* 2020; 20: 22.
11. Saum K, et al.: *J Am Geriatr Soc* 2017; 65: e27–e32.
12. Schneider J, et al.: *Front Pharmacol* 2021; 12: 686990.
13. Schöttker B, et al.: *Eur J Clin Pharmacol* 2017; 73: 1041–8.
14. De Vries FM, et al.: *Br J Clin Pharmacol* 2021; 87: 2732–56.
15. Knopf H, Grams D: *Bundesgesundheitsblatt Gesundheitsforschung Gesundheitsschutz* 2013; 56: 868–77.
16. Katzke VA, et al.: *Sci Rep* 2024; 14: 106.
17. Lappe V, et al.: *Pharmacoepidemiology* 2022; 1: 12–25.
18. Rach S, et al.: *Eur J Epidemiol* 2025; 40: 475–89.
19. Guillot J, et al.: *Therapie* 2020; 75: 407–16.
20. Nishtala PS, Salahudeen MS: *Gerontology* 2015; 61: 195–202.
21. Wilson EB: *J Am Stat Assoc* 1927; 22: 209–12.
22. <https://dplyr.tidyverse.org>
23. <https://r-datatable.com>
24. FE Harrell, Jr: Springer Cham Heidelberg New York Dordrecht London 2015.
25. <https://www.tk.de/resource/blob/2196082/f604537af1607d536bc577895e113368/gesundheitsreport-arz-neimittelverordnungen-2025-data.pdf>
26. von Buedingen F, et al.: *BMC Fam Pract* 2018; 19: 131.
27. Kutner JS, et al.: *JAMA Intern Med* 2015; 175: 691–700.
28. Farrell B, et al.: *PLoS One* 2016; 11: e0161248.
29. Peters A, et al.: *Eur J Epidemiol* 2022; 37: 1107–24.

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Supplementary material

Complete list of full references, eSupplement:
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Supplementary material to accompany the article

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Complete list of full references

- Chang TI, Park H, Kim DW, et al.: Polypharmacy, hospitalization, and mortality risk: A nationwide cohort study. *Sci Rep* 2020; 10: 18964.
- Sheppard JP, Temple E, Wang A, et al.: Effect of antihypertensive deprescribing on hospitalisation and mortality: Long-term follow-up of the OPTIMISE randomised controlled trial. *Lancet Healthy Longev* 2024; 5: e563–73.
- Masnoon N, Shakib S, Kalisch-Ellett L, Caughey GE: What is polypharmacy? A systematic review of definitions. *BMC Geriatr* 2017; 17: 230.
- Delara M, Murray L, Jafari B, et al.: Prevalence and factors associated with polypharmacy: A systematic review and meta-analysis. *BMC Geriatr* 2022; 22: 601.
- Bennie M, Santa-Ana-Tellez Y, Galistiani GF, et al.: The prevalence of polypharmacy in older Europeans: A multi-national database study of general practitioner prescribing. *Br J Clin Pharmacol* 2024; 90: 2124–36.
- Dörks M, Herget-Rosenthal S, Schmiemann G, Hoffmann F: Polypharmacy and renal failure in nursing home residents: Results of the inappropriate medication in patients with renal insufficiency in nursing homes (IMREN) study. *Drugs Aging* 2016; 33: 45–51.
- Junius-Walker U, Theile G, Hummers-Pradier E: Prevalence and predictors of polypharmacy among older primary care patients in Germany. *Fam Pract* 2007; 24: 14–9.
- Kostev K, Hagemann-Goebel M, Gessler N, et al.: Is there an association between depression, anxiety disorders and COVID-19 severity and mortality? A multicenter retrospective cohort study conducted in 50 hospitals in Germany. *J Psychiatr Res* 2023; 157: 192–6.
- Midão L, Giardini A, Menditto E, Kardas P, Costa E: Polypharmacy prevalence among older adults based on the survey of health, ageing and retirement in Europe. *Arch Gerontol Geriatr* 2018; 78: 213–20.
- Mielke N, Huscher D, Douros A, et al.: Self-reported medication in community-dwelling older adults in Germany: Results from the Berlin Initiative Study. *BMC Geriatr* 2020; 20: 22.
- Saum K, Schöttker B, Meid AD, et al.: Is polypharmacy associated with frailty in older people? Results from the ESTHER cohort study. *J Am Geriatr Soc* 2017; 65: e27–e32.
- Schneider J, Algharably EAE, Budnick A, Wenzel A, Dräger D, Kreutz R: High prevalence of multimorbidity and polypharmacy in elderly patients with chronic pain receiving home care are associated with multiple medication-related problems. *Front Pharmacol* 2021; 12: 686990.
- Schöttker B, Saum KU, Muhlack DC, Hoppe LK, Holleczer B, Brenner H: Polypharmacy and mortality: New insights from a large cohort of older adults by detection of effect modification by multi-morbidity and comprehensive correction of confounding by indication. *Eur J Clin Pharmacol* 2017; 73: 1041–8.
- De Vries FM, Stingl JC, Breteler MMB: Polypharmacy, potentially inappropriate medication and pharmacogenomics drug exposure in the Rhineland Study. *Br J Clin Pharmacol* 2021; 87: 2732–56.
- Knopf H, Grams D: [Medication use of adults in Germany: results of the German Health Interview and Examination Survey for Adults (DEGS1)]. *Bundesgesundheitsblatt Gesundheitsforschung Gesundheitsschutz* 2013; 56: 868–77.
- Katzke VA, Bajracharya R, Nasser MI, Schöttker B, Kaaks R: Number of medically prescribed pharmaceutical agents as predictor of mortality risk: A longitudinal, time-variable analysis in the EPIC-Heidelberg cohort. *Sci Rep* 2024; 14: 106.
- Lappe V, Dinh TS, Harder S, et al.: Multimедication guidelines: Assessment of the size of the target group for medication review and description of the frequency of their potential drug safety problems with routine data. *Pharmacoepidemiology* 2022; 1: 12–25.
- Rach S, Sand M, Reineke A, et al.: The baseline examinations of the German National Cohort (NAKO): Recruitment protocol, response, and weighting. *Eur J Epidemiol* 2025; 40: 475–89.
- Guillot J, Maumus-Robert S, Bezin J: Polypharmacy: A general review of definitions, descriptions and determinants. *Therapie* 2020; 75: 407–16.
- Nishtala PS, Salahudeen MS: Temporal trends in polypharmacy and hyperpolypharmacy in older New Zealanders over a 9-year period: 2005–2013. *Gerontology* 2015; 61: 195–202.
- Wilson EB: Probable inference, the law of succession, and statistical inference. *J Am Stat Assoc* 1927; 22: 209–12.
- Wickham H, François R, Henry L, Müller K, Vaughan D: dplyr: A grammar of data manipulation. *dplyr: A grammar of data manipulation*. <https://dplyr.tidyverse.org> (last accessed on 04 July 2026).
- Barrett T, Dowle M, Srinivasan A, et al.: data.table: Extension of „data.frame“. *data.table: Extension of „data.frame“*. <https://r-datatable.com> (last accessed on 04 July 2026).
- FE Harrell, Jr: Regression modeling strategies: With applications to linear models, logistic and ordinal regression, and survival analysis. 2nd edition. Springer Cham Heidelberg New York Dordrecht London 2015.
- Grobe T, Bessel S: Gesundheitsreport 2025—Arzneiverordnungen: www.tk.de/resource/blob/2196082/f604537af1607d536bc577895e113368/gesundheitsreport-arzneimittelverordnungen-2025-data.pdf (last accessed on 04 July 2026).
- von Buedingen F, Hammer MS, Meid AD, Müller WE, Gerlach FM, Muth C: Changes in prescribed medicines in older patients with multimorbidity and polypharmacy in general practice. *BMC Fam Pract* 2018; 19: 131.
- Kutner JS, Blatchford PJ, Taylor DH, et al.: Safety and benefit of discontinuing statin therapy in the setting of advanced, life-limiting illness: A randomized clinical trial. *JAMA Intern Med* 2015; 175: 691–700.
- Farrell B, Pottie K, Rojas-Fernandez CH, Bjerre LM, Thompson W, Welch V: Methodology for developing deprescribing guidelines: Using evidence and GRADE to guide recommendations for deprescribing. *PLoS One* 2016; 11: e0161248.
- Peters A, German National Cohort (NAKO) Consortium, Peters A, et al.: Framework and baseline examination of the German National Cohort (NAKO). *Eur J Epidemiol* 2022; 37: 1107–24.

Polypharmacy among 200,000 participants of the population based
German National Cohort Study (NAKO) study – Baseline Analysis
Supplementary material

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61 **Methods – Medications excluded from the polypharmacy count and identification of determinants**
62 **of polypharmacy**

63

64 *Medications excluded from the count*

65 **Table S1: Medications (ATC Codes and ATC groups) excluded from the count**

Medication group	ATC code
Food supplements	A11, A12, V06, A02X, C10AX06 NAKO special codes TETO, DIET, NEM, GIT, PROT
Homeopathic or anthroposophical drugs	A01AH, A02XH, A03AH, A03HH, A04AH, A05AH, A05BH, A07XH, A08AH, A09AH, A10XH, A12AH, A12CH, A13AH^, B03XH, C01AH, C01CH, C01EH, C02KH, C03XH, C04AH, C05AH, C05CH, C06AH, D03AH, D04AH, D05BH, D10BH, D11BH, G02CH, G04BH, G04CH, H03BH, H05AH, L01CH, L03AH, M01BH, M02AH, M04AH, M09AH, N01BH, N02BH, N02CH, N04AH, N05H, N06AH, N07CH^, N07XH, R01AH, R01BH, R02AH, R03DH, R04AH, R05CH, R05FH, R05XH, R07AH, S01XH, S02DH, V60 NAKO special code ALT
Non-systemic drugs	A03AP, C05AP, R05DP, D02, D03, D04, D08, D09, D11, R02, R04, S01, V04, V07, V08, V09, V20, D01A, D06A, M02B, P03A, P03B, A01AA, A01AP, D07AA, D07BA, D07CA, D07XA, G02CD, M09AX, S02DC, C10AX13 NAKO special code DER
Other	NAKO special code SON

66

67 *Determinants of polypharmacy*

68 Logistic regression models were used to estimate adjusted odds ratios (aORs) with 95% CI for the
69 association between sociodemographic variables (e.g. age, sex, education, income), comorbidities
70 (e.g. self-reported medical history of several cardiovascular diseases, diabetes, depression, anxiety)
71 and lifestyle factors (e.g. alcohol consumption, smoking) and polypharmacy using complete case
72 data. Variable selection was informed by previous studies(1).

73 Sociodemographic covariates included in the analysis were sex, age in years (restricted cubic splines
74 with 4 knots were used to model the non-linear association between age and polypharmacy status),
75 income group (< 60% of monthly net equivalent income (i.e. at risk of poverty), 60% - < 100% of
76 monthly net equivalent income, ≥ 100% of monthly net equivalent income), and education in
77 International Standard Classification of Education categories (low – ISCED 97 levels 0-2, medium –
78 ISCED 97 levels 3-4, high – ISCED 97 levels 5-6, not finished - still attending school, university, or an

79 apprenticeship). Several variables to assess the presence of chronic comorbidities, each defined as
80 ever being diagnosed with the respective condition, were also included (see table 1 in the main text
81 for a complete list). Presence of an epilepsy diagnosis was assessed based on an algorithm developed
82 by members of the NAKO expert group neurological and psychiatric disorders. Based on self-reported
83 diagnosis, being treated for epilepsy in the last 12 months, time since the first diagnosis of epilepsy,
84 and use of antiepileptic medicines (ATC N03), participants were classified as either not being
85 diagnosed with epilepsy, having a possible diagnosis of epilepsy, or very likely having a diagnosis of
86 epilepsy. Presence of depressive symptoms was assessed using the results of the PHQ-9
87 questionnaire and categorized as no depressive symptoms (PHQ-9 sum score < 10) and depressive
88 symptoms (PHQ-9 sum score $\geq$ 10). Presence of symptoms of anxiety was included using the results
89 of the Generalized Anxiety Disorder Scale-7 (GAD-7) and categorized as no or mild symptoms (GAD-7
90 sum score < 10) and moderate or severe symptoms (GAD-7 sum score $\geq$ 10). A detailed description of
91 the questionnaires and scales used to assess psychiatric disorders in the NAKO was published
92 elsewhere (1, 2). As the NAKO only includes information about selected comorbidities, self-rated
93 health, assessed using the WHOQOL-BREF(3, 4) (categorized as excellent, very good, good, fair, poor)
94 was included as a proxy for overall health status. Furthermore, the following lifestyle factors were
95 included in the model: Risky alcohol consumption (AUDIT-C score > 4 for men and > 3 for women),
96 smoking (never, former, current), and BMI category (underweight, normal weight, overweight,
97 obesity). In the NAKO BMI categories were defined using the WHO standards: Underweight: BMI
98 < 18.5, normal weight: BMI $\geq$ 18.5 to < 25.0, overweight: BMI $\geq$ 25 to < 30.0, obesity: BMI $\geq$ 30.
99

Table S2: Characteristics of the 203,765 NAKO participants included in the analysis stratified by polypharmacy status.

	Overall (n, %)	Polypharmacy (≥ 5 drugs) (n, %)	Hyperpolypharmacy (≥ 10 drugs) (n, %)
N	203,765	14,995 (7.4)	1,227 (0.6)
Age (mean, SD)	49.8 (12.8)	60.5 (8.1)	61.4 (7.3)
Female	102,733 (50.4)	6,869 (45.8)	505 (41.2)
Income			
< 60% of MNEI	28,213 (14.9)	3,261 (23.3)	397 (34.3)
60% -< 80% of MNEI	27,357 (14.4)	2,898 (20.7)	256 (22.1)
80% -< 100% of MNEI	27,174 (14.3)	1,951 (13.9)	138 (11.9)
100% -< 150% of MNEI	58,828 (31.0)	3,612 (25.8)	242 (20.9)
≥ 150% of MNEI	48,321 (25.4)	2,297 (16.4)	126 (10.9)
Level of education			
Low	5,161 (2.7)	775 (5.6)	83 (7.5)
Medium	77,971 (41.2)	6,920 (50.4)	582 (52.8)
High	102,013 (53.9)	6,005 (43.8)	437 (39.6)
Not finished	4,269 (2.3)	19 (0.1)	1 (0.1)
Self-rated health ¹			
Excellent	7,282 (3.7)	77 (0.6)	6 (0.5)
Very good	57,988 (29.6)	677 (4.9)	20 (1.8)
Good	108,264 (55.3)	7,533 (54.1)	347 (31.7)
Less good	20,356 (10.4)	4,935 (35.4)	565 (51.6)
Poor	1,798 (0.9)	706 (5.1)	156 (14.3)
Self-report of doctor's diagnosis of			
Any allergy	87,758 (42.7)	6,386 (42.3)	577 (46.5)
Arterial hypertension	56,649 (27.5)	11,737 (78.2)	1,069 (87.1)
Backpain (daily for more than three months)	50,576 (24.5)	6,420 (42.6)	708 (57.4)
High blood lipids	49,990 (23.7)	8,766 (57.8)	898 (72.6)
Osteoarthritis	48,749 (23.3)	7,047 (46.4)	699 (56.1)

Thyroid disease	44,350 (21.3)	5,819 (38.5)	551 (44.7)
Heartburn	36,324 (17.4)	5,507 (36.4)	553 (44.6)
Cardiac arrhythmia	20,035 (9.1)	4,013 (25.8)	84 (38.7)
Asthma	18,168 (8.4)	2,285 (14.6)	260 (20.6)
Any cancer	15,495 (7.3)	2,199 (14.3)	200 (16.2)
Diabetes	12,789 (6.0)	5,300 (35.1)	804 (65.2)
Chronic bronchitis or COPD	11,731 (5.2)	2,384 (15.2)	335 (26.6)
Peptic ulcer	11,332 (5.2)	1,852 (11.9)	220 (17.2)
Gout or other uric acid disease	9,779 (4.3)	2,793 (17.8)	411 (32.4)
Osteoporosis	7,420 (3.1)	1,479 (9.0)	200 (15.0)
Heart failure	6,671 (2.6)	2,559 (15.1)	423 (32.6)
Coronary heart disease / angina pectoris	6,357 (2.6)	3,249 (20.2)	440 (34.1)
Limited kidney function or renal insufficiency	5,334 (2.2)	1,355 (8.3)	268 (21.1)
Peripheral arterial disease (of the extremities)	4,780 (1.8)	1,578 (9.3)	254 (19.5)
Myocardial infarction	3,957 (1.7)	2,232 (14.4)	270 (21.6)
Ulcerative colitis or Crohn's Disease	3,114 (1.1)	459 (2.3)	40 (2.4)
Psychiatric disorders			
Anxiety ²	9,779 (5.2)	1,240 (9.8)	167 (17.4)
Depression ³	14,879 (7.9)	2,130 (16.8)	279 (29.0)
Neurologic disorders ⁴			
Epilepsy - no diagnosis	201,675 (99.3)	14,621 (97.8)	1,174 (95.9)
Epilepsy - possible diagnosis	1,002 (0.5)	249 (1.7)	40 (3.3)
Epilepsy - very likely diagnosis	437 (0.2)	77 (0.5)	10 (0.8)
Risky alcohol consumption ⁵	68,956 (35.5)	4,001 (29.3)	213 (20.0)
Smoking			
Never	90,120 (46.2)	4,632 (33.6)	332 (30.9)
Former	40,019 (20.5)	2,697 (19.6)	213 (19.8)
Current	65,010 (33.3)	6,447 (46.8)	531 (49.3)
Body mass index			
Underweight	2,131 (1.1)	46 (0.3)	2 (0.2)

Normal weight	80,230 (40.5)	2,133 (14.9)	103 (9.0)
Overweight	73,110 (36.9)	4,826 (33.8)	281 (24.6)
Obesity	42,682 (21.5)	7,290 (51.0)	755 (66.2)

Notes: The upper age limit at recruitment was 69 years. As baseline examinations were conducted over several years (2014–2019), some participants reached or exceeded the age of 70 by the time of their baseline assessment. All drugs taken in the seven days before the baseline examination were assessed by computer-assisted, face-to-face interviews to which participants were asked to bring packages of the medications they used. Polypharmacy was defined as regular use of five or more medications.

Hyperpolypharmacy was defined as regular use of ten or more medications. MNEI: monthly net equivalent income. ¹Assessed using the WHOQOL-BREF. ²Presence of symptoms of anxiety was assessed using the results of the Generalized Anxiety Disorder Scale-7 (GAD-7). ³Presence of depressive symptoms was assessed using the results of the PHQ-9 questionnaire. ⁴Presence of an epilepsy diagnosis was assessed based on an algorithm developed by members of the NAKO expert group neurological and psychiatric disorders based on self-reported diagnosis, being treated for epilepsy in the last 12 months, time since the first diagnosis of epilepsy, and use of antiepileptic medicines (ATC N03).

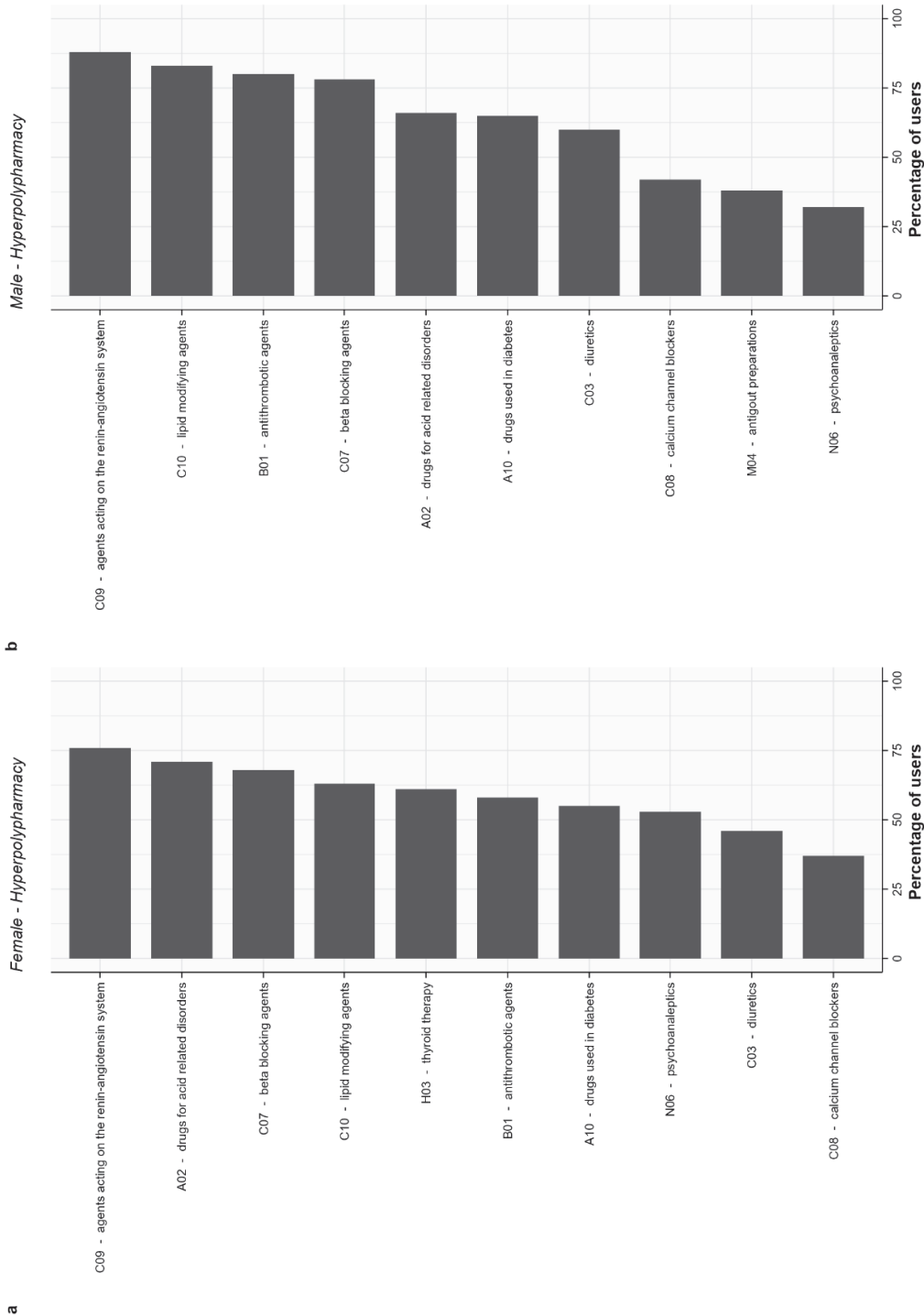
⁵Assessed using the AUDIT-C score.

109 **Table S3: Proportions of participants exposed to polypharmacy and hyperpolypharmacy in the total study population and stratified by sex and age group.**
110 **All drugs (regularly taken and taken on demand).**

	Study Population	Polypharmacy			Hyperpolypharmacy		
		N _{User}	Percent _{User}	95% CI	N _{User}	Percent _{User}	95% CI
All participants	204,218	21,610	10.6	(10.4-10.7)	2,097	1.03	(0.98-1.07)
Female	102,999	11,316	11.0	(10.8-11.2)	1,013	0.98	(0.93-1.05)
Male	101,219	10,294	10.2	(10.0-10.4)	1,084	1.07	(1.01-1.14)
Age group							
18 - 29 Years	19,930	340	1.7	(1.5-1.9)	17	0.09	(0.05-0.14)
30 - 39 Years	21,596	610	2.8	(2.6-3.1)	26	0.12	(0.08-0.18)
40 - 49 Years	52,892	2,657	5.0	(4.8-5.2)	168	0.32	(0.27-0.37)
50 - 59 Years	54,791	5,889	10.7	(10.5-11.0)	560	1.02	(0.94-1.11)
60 - 69 Years	50,644	10,829	21.4	(21.0-21.7)	1,166	2.30	(2.18-2.44)
70 - 74 Years	4,365	1,285	29.4	(28.1-30.8)	160	3.67	(3.15-4.27)

Notes: For better readability, values for hyperpolypharmacy have been rounded to two decimal places. All drugs taken in the seven days before the baseline examination were assessed by computer-assisted, face-to-face interviews to which participants were asked to bring packages of the medications they used. Polypharmacy was defined as regular use of five or more medicines. Hyperpolypharmacy was defined as regular use of ten or more medicines. For a list of medications excluded from the polypharmacy count, the reader is referred to table S1 in the supplementary material.

111 **Figure S1 Top ten drug classes used by females and males with hyperpolypharmacy.**



Results - Determinants of polypharmacy

Table S4 shows the results of the logistic regression model. The aim of this multivariable analysis was not to develop a predictive model, but to estimate the association between predefined determinants and polypharmacy while adjusting for potential confounding factors. The analysis included non-modifiable determinants, including age, sex, and comorbidities as well as modifiable factors such as smoking behavior and alcohol consumption. Females had higher odds of polypharmacy compared to males (aOR = 1.20, 95% CI (1.14-1.26)). While the proportion of polypharmacy was higher among men (Table 2 in the main manuscript), adjustment for age and comorbidity burden reversed this association, indicating that female sex was independently associated with polypharmacy at comparable levels of morbidity. The effect of age on the probability of reporting polypharmacy is shown in figure S2. The probability of reporting polypharmacy gradually increased up to the age of 40 and more sharply thereafter. Compared with participants at risk of poverty, participants of the highest income group were more likely to experience polypharmacy. The slightly higher likelihood of polypharmacy among individuals with higher income may reflect differences in healthcare utilisation and access to medical care, potentially leading to higher rates of diagnosis and treatment of chronic conditions rather than overtreatment.

Compared with participants who rated their health as excellent, those who saw themselves as being in good, fair, or poor health had higher odds of polypharmacy. Almost all comorbidities included in the model increased the odds of polypharmacy. The odds of polypharmacy were 3.7 times higher (aOR = 3.71, (3.29-4.18)) in participants who reported a previous diagnosis of myocardial infarction, 2.7 times higher (aOR = 2.74, (2.58-2.91)) in participants with a self-reported diagnosis of diabetes, and 2.4 times higher (aOR = 2.37, (2.26-2.48)) in patients who reported being diagnosed with arterial hypertension, compared to participants who did not report the respective diagnosis. This is consistent with the high proportion of cardiovascular drug users (Figure 1 in the main manuscript) and in line with previous European studies investigating determinants of polypharmacy (5–7). Among the psychiatric and neurologic conditions included in the analyses, a previous self-reported diagnosis

of epilepsy and presence of depression increased the odds of experiencing polypharmacy. These findings are supported by previous studies that described a high comorbidity burden among patients with epilepsy (8) and depression (9). Overall, the comorbidities associated with higher odds of polypharmacy are consistent with multimorbidity patterns in Germany identified in previous studies (10–12).

Compared with normal weight, the odds ratios were 0.90 (0.69-1.18) for underweight, 0.86 (0.67-1.14) for overweight, and 1.06 (0.82-1.40) for obesity, indicating no clear independent association between BMI category and polypharmacy. In the regression model, BMI was included as a categorical variable, whereas most comorbidities (e.g., diabetes or cardiovascular diseases) were included as binary indicators. Consequently, the estimated odds ratios reflect the effect of changing a weight category, which represents a much smaller change in health status compared with the presence versus absence of a chronic disease. In addition, part of the association between obesity and polypharmacy may be mediated through obesity-related conditions such as diabetes and cardiovascular diseases, which were included separately in the model. Adjusting for these conditions may therefore attenuate the independent association between BMI and polypharmacy.

Table S4: Determinants of polypharmacy in the NAKO.

Parameter	Adj. Odds	
	ratio	95% CI
(Intercept)	0.01	(0.00-0.01)
<i>Sociodemographic factors</i>		
Sex		
Male	(reference)	
Female	1.20	(1.14-1.26)

Income

< 60% of MNEI	(reference)	
60% -< 80% of MNEI	1.02	(0.95-1.11)
80% -< 100% of MNEI	1.06	(0.98-1.15)
100% -< 150% of MNEI	1.04	(0.97-1.11)
≥ 150% of MNEI	1.15	(1.07-1.24)

Level of education

Low	1.02	(0.90-1.17)
Medium	0.96	(0.84-1.10)
High	(reference)	
Not finished	0.95	(0.64-1.36)

Comorbidities and self-rated health

Medical history of

Any allergy	1.06	(1.02-1.11)
Myocardial infarction	3.71	(3.29-4.18)
Coronary heart disease / angina pectoris	2.35	(2.13-2.59)
Heart failure	1.24	(1.12-1.37)
Cardiac arrhythmia	1.40	(1.32-1.49)
Peripheral arterial disease (of the extremities)	1.36	(1.21-1.53)
Arterial hypertension	2.37	(2.26-2.48)

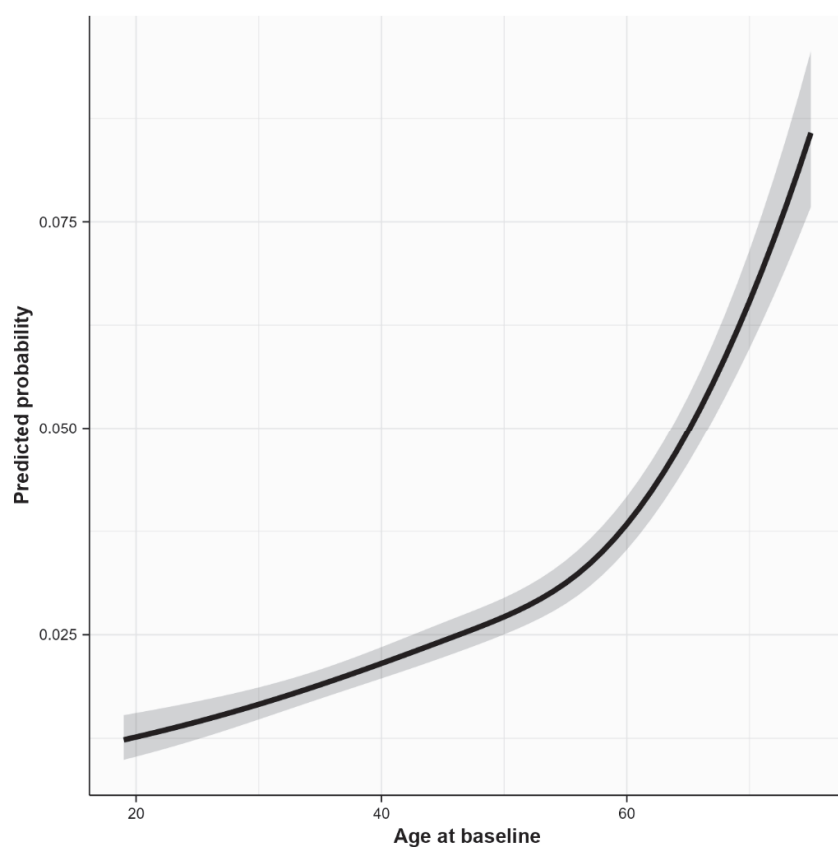
Diabetes	2.74	(2.58-2.91)
High blood fat levels	1.39	(1.33-1.45)
Gout or other uric acid disease	1.46	(1.35-1.58)
Thyroid disease	1.64	(1.56-1.72)
Chronic bronchitis or COPD	1.23	(1.14-1.33)
Asthma	1.43	(1.34-1.54)
Peptic ulcer	1.00	(0.93-1.08)
Heartburn	1.37	(1.31-1.44)
Ulcerative colitis or Crohn's Disease	1.70	(1.45-1.98)
Backpain (daily for more than three months)	1.05	(1.00-1.10)
Osteoporosis	1.39	(1.27-1.52)
Osteoarthritis	1.07	(1.02-1.13)
Limited kidney function or renal insufficiency	1.15	(1.03-1.29)
Any cancer	1.29	(1.21-1.38)
Depression	1.24	(1.14-1.35)
Anxiety		
No or mild symptoms	(reference)	
Moderate or severe symptoms	0.94	(0.85-1.04)
Epilepsy		
No diagnosis	(reference)	

Possible diagnosis	2.32	(1.85-2.88)
Very likely diagnosis	1.63	(1.09-2.39)
Self-rated health		
Excellent	(reference)	
Very good	0.93	(0.75-1.15)
Good	1.48	(1.21-1.83)
Less good	2.70	(2.19-3.36)
Poor	2.88	(2.22-3.76)
<i>Lifestyle factors</i>		
Risky alcohol consumption	0.93	(0.88-0.97)
Smoking		
Never	(reference)	
Current	1.03	(0.97-1.10)
In the past	1.13	(1.08-1.19)
Body mass index		
Normal weight	(reference)	
Underweight	0.90	(0.69-1.18)
Overweight	0.86	(0.67-1.14)
Obesity	1.06	(0.82-1.40)

155 Notes: Multivariate logistic regression model to estimate the association between polypharmacy and
156 covariates. Restricted cubic splines with four knots were used to model the non-linear association between age

157 and polypharmacy status. The partial effect of age on the probability of reporting polypharmacy is shown in
158 figure S2. Polypharmacy was defined as regular use of five or more medicines. MNEI: monthly net equivalent
159 income.
160

161 **Figure S2: Partial effect of age on the probability of reporting polypharmacy.**



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165 **References**

- 166 1. Guillot J, Maumus-Robert S, Bezin J: Polypharmacy: A general review of definitions, descriptions
167 and determinants. *Therapies* 2020; 75: 407–16.
- 168 2. Erhardt A, Gelbrich G, Klinger-König J, et al.: Generalised anxiety and panic symptoms in the
169 German National Cohort (NAKO). *World J Biol Psychiatry* 2023; 24: 881–96.
- 170 3. Streit F, Zillich L, Frank J, et al.: Lifetime and current depression in the German National Cohort
171 (NAKO). *World J Biol Psychiatry* 2023; 24: 865–80.
- 172 4. Hoffmann W, Jöckel K-H, Kaaks R, Wichmann H-E, Greiser KH, Linseisen J: The national cohort. A
173 prospective epidemiologic study resource for health and disease research in Germany.
- 174 5. Angermeyer MC, Kilian R, Matschinger H: WHOQOL - 100 und WHOQOL - BREF: Handbuch für die
175 deutschsprachige Version der WHO-Instrumente zur Erfassung von Lebensqualität. Hogrefe
176 2000.
- 177 6. Abolhassani N, Castioni J, Marques-Vidal P, Vollenweider P, Waeber G: Determinants of change
178 in polypharmacy status in Switzerland: the population-based CoLaus study. *Eur J Clin Pharmacol*
179 2017; 73: 1187–94.
- 180 7. Calderón-Larrañaga A, Gimeno-Feliu LA, González-Rubio F, et al.: Polypharmacy Patterns:
181 Unravelling Systematic Associations between Prescribed Medications. Carvajal A (ed.): *PLoS ONE*
182 2013; 8: e84967.
- 183 8. Veehof L, Stewart R, Haaijer-Ruskamp F, Jong BM -d.: The development of polypharmacy. A
184 longitudinal study. *Fam Pract* 2000; 17: 261–7.
- 185 9. Uepping P, Hamer H, Scholten J, Kostev K: Physical and mental health comorbidities of patients
186 with epilepsy in Germany – A retrospective cohort study. *Epilepsy Behav* 2021; 117: 107857.
- 187 10. Steffen A, Nübel J, Jacobi F, Bätzing J, Holstiege J: Mental and somatic comorbidity of depression:
188 a comprehensive cross-sectional analysis of 202 diagnosis groups using German nationwide
189 ambulatory claims data. *BMC Psychiatry* 2020; 20: 142.
- 190 11. Amirzada M, Buczak-Stec E, König H-H, Hajek A: Multimorbidity patterns in the German general
191 population aged 40 years and over. *Arch Gerontol Geriatr* 2023; 114: 105067.
- 192 12. Van Den Bussche H, Koller D, Kolonko T, et al.: Which chronic diseases and disease combinations
193 are specific to multimorbidity in the elderly? Results of a claims data based cross-sectional study
194 in Germany. *BMC Public Health* 2011; 11: 101.
- 195 13. Fuchs J, Busch M, Lange C, Scheidt-Nave C: Prevalence and patterns of morbidity among adults in
196 Germany: Results of the German telephone health interview survey German Health Update
197 (GEDA) 2009. *Bundesgesundheitsblatt - Gesundheitsforschung - Gesundheitsschutz* 2012; 55:
198 576–86.

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