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Characteristics associated with polypharmacy in people with type 2 diabetes: the Dutch Diabetes Pearl cohort

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Abstract

Aim: To describe the prevalence and characteristics of polypharmacy in a Dutch cohort of individuals with type 2 diabetes.

Methods: We included people with type 2 diabetes from the Diabetes Pearl cohort, of whom 3886 were treated in primary care and 2873 in academic care (secondary/tertiary). With multivariable multinomial logistic regression analyses stratified for line of care, we assessed which sociodemographic, lifestyle and cardiometabolic characteristics were associated with moderate (5–9 medications) and severe polypharmacy (≥10 medications) compared with no polypharmacy (0–4 medications).

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Centers. The funding body had no role in designing the study or in collecting, analysing, or interpreting data.

Results: Mean age was 63 ± 10 years, and 40% were women. The median number of daily medications was 5 (IQR 3–7) in primary care and 7 (IQR 5–10) in academic care. The prevalence of moderate and severe polypharmacy was 44% and 10% in primary care, and 53% and 29% in academic care respectively. Glucose-lowering and lipid-modifying medications were most prevalent. People with severe polypharmacy used a relatively large amount of other (i.e. non-cardiovascular and non-glucose-lowering) medication. Moderate and severe polypharmacy across all lines of care were associated with higher age, low educational level, more smoking, longer diabetes duration, higher BMI and more cardiovascular disease.

Conclusions: Severe and moderate polypharmacy are prevalent in over half of people with type 2 diabetes in primary care, and even more in academic care. People with polypharmacy are characterized by poorer cardiometabolic status. These results highlight the significance of polypharmacy in type 2 diabetes.

1 | INTRODUCTION

Treatment of type 2 diabetes generally requires a prescription of medication for glycaemic control, cardiovascular risk management and common comorbidities. Consequently, people with type 2 diabetes are prone to polypharmacy and severe polypharmacy, i.e. the prescription of five or more and 10 or more unique medications respectively.[1] The estimated prevalence of polypharmacy among people with type 2 diabetes varies from 57% to 99%.[1–10] Above and beyond negative consequences related to type 2 diabetes and its comorbidities, polypharmacy is independently associated with not taking prescribed medication (non-adherence),[11] inappropriate prescriptions,[12,13] adverse drug reactions,[14] and high risk of hospitalization and high mortality rates.[15,16] Furthermore, polypharmacy in type 2 diabetes is associated with suboptimal glycaemic control,[17] which in turn increases the risk of long-term complications of diabetes.[18,19]

Previous studies among people with type 2 diabetes have identified several characteristics associated with polypharmacy, such as age,[1,7,8] female sex,[1,6] low educational level,[7] higher BMI,[6] longer diabetes duration[6,8] and prior cardiovascular disease (CVD).[1,6] However, studies investigating the prevalence of polypharmacy[1–10] or its characteristics[1,6–8] have been mainly performed in selected type 2 diabetes populations, consisting of older adults[3–6,10] or people treated either in specialized[1,2,7] or primary care settings.[9] Moreover, lifestyle-related factors were not included as potential associated characteristics in these studies, although these characteristics have been associated with polypharmacy in the general population.[20,21]

In this study, we assessed the relationship of these different characteristics, synchronously, with risk of polypharmacy in a Dutch cohort of individuals with type 2 diabetes, treated in different geographical areas and care settings (i.e. primary or academic care). In addition, we investigated the prevalence of polypharmacy across different lines of care and the associations of medication subtypes with polypharmacy in people with type 2 diabetes.

What's new?

- Polypharmacy is a risk factor for not taking medicine, inappropriate prescriptions and mortality. The literature lacks knowledge on how people with type 2 diabetes and polypharmacy are characterized in different care settings.
- We found that polypharmacy exists in over half of people with type 2 diabetes in primary care, and even more in academic care. People with polypharmacy across all lines of care are older, less educated, and have an unhealthier lifestyle and a poorer cardiometabolic health.
- Regular reviews of the necessity of all medication, potential interactions and whether all medication is taken remain important to optimize the treatment of people with type 2 diabetes.

2 | METHODS

2.1 | Study population

This study is part of the Parelsnoer Initiative, a partnership between all eight university medical centres in the Netherlands. The Dutch Diabetes Pearl is a national, observational cohort study of people with type 2 diabetes,

who are treated in primary, secondary or tertiary care, in different geographical areas in the Netherlands. In the Netherlands, the majority of people with type 2 diabetes is treated in primary care, i.e. in general practice. People with poorly controlled diabetes or complex comorbidities can be referred to hospitals in the area (non-academic or academic) for their diabetes treatment (secondary care). In addition, non-academic hospitals can refer to academic hospitals if needed (tertiary care). The Diabetes Pearl cohort consists of people treated in primary, secondary or tertiary care, and is oversampled for people treated in academic hospitals (secondary or tertiary care). Data were collected between 2009 and 2015. All university medical ethical committees approved this study (reference number NL27783.029.09). All participants provided written informed consent. Further details on the design of the Dutch Diabetes Pearl have been published previously.[22]

People were eligible for participation if they were diagnosed with type 2 diabetes and received secondary or tertiary care in one of the academic medical centres of Amsterdam, Utrecht, Nijmegen, Rotterdam, Leiden or Groningen, if they received primary medical care in the area of Hoorn, or if they received primary, secondary or tertiary care in the area of Maastricht. Not being able to understand and write the Dutch language was an exclusion criterion.

In total, 7013 people were included in the Diabetes Pearl cohort. We included 6759 people in the current study, after exclusion of 197 participants whose data regarding medication use were unavailable and 57 participants from Maastricht whose line of care was unavailable.

All data were collected via standard operating procedures to ensure comparability of the data collected, during a 2-h visit to each of the eight participating clinics.

2.2 | Medication and polypharmacy levels

Information on current medication use was recorded via dispensing labels or provided through lists from pharmacists. The number of medications was defined as the number of concomitantly used, unique medications, including non-systemic and over-the-counter medications. Fixed dose combinations were counted by their number of active pharmaceutical ingredients. The number of medications were categorized into three levels of polypharmacy according to cut-off values previously used in the literature[1]: no polypharmacy (0–4 medications), moderate polypharmacy (5–9 medications), and severe polypharmacy (10 or more medications).

Medication was classified using the Anatomical Therapeutic Chemical (ATC) classification system.[23] We defined three main subgroups in medication types: (1) glucose-lowering medication (ATC-code: A10), (2) cardiovascular medication (ATC codes: B01; C01-C04; C07-C10) and (3) other medication (all remaining ATC codes).

We also collected data on sociodemographic, lifestyle and cardiometabolic characteristics.

2.3 | Sociodemographic characteristics

Age (years), sex (men/women) and line of care (primary care/academic care) were collected from hospital information systems. Educational level was self-reported based on highest ascertainment and stratified into: low (no education, primary education or practical training); middle (prevocational secondary education, vocational training, general secondary education or pre-university education); and high (professional university education, university). Ethnicity was estimated based on country of birth or judged by study nurses based on conversations during which participants were asked about their ethnicity, as described previously.[24] For this study, we categorized ethnicity as white North European or non-white North European.

2.4 | Lifestyle characteristics

Information about smoking history was self-reported and categorized into never smokers, current smokers and former smokers. Alcohol consumption was self-reported as average alcohol consumption per week and categorized as no alcohol consumption, light-to-moderate alcohol consumption (>0 to <14 glasses/week) and heavy alcohol consumption (≥14 glasses/week).[25]

2.5 | Cardiometabolic characteristics

Diabetes duration (years) was calculated from the self-reported date of diabetes onset and the date of inclusion. Information on prior CVD was obtained via a modified Rose Questionnaire,[26] and defined as a self-reported history of myocardial infarction, stroke, intermittent claudication, angina pectoris, vascular surgery or angioplasty.

BMI (kg/m^2) was defined as a person's weight (kg) divided by the square of height (m). Blood pressure (mmHg) was measured three times on the right arm after 10 min of seated rest, using a non-invasive blood pressure monitor (Omron 7051 T in seven centres, Colin Press BP 8800p in one centre). Final systolic blood pressures (SBP) were calculated as mean of the successive measurements.

HbA_{1c} levels [mmol/mol (%)], serum creatinine (μmol/l) and LDL cholesterol (mmol/l) were assessed from fasting venous blood samples. HbA_{1c} levels were categorized into three

groups: <54 mmol/mol (< 7.1%), 54–64 mmol/mol (7.1–8.0%) and >64 mmol/mol (> 8.0%). The eGFR (ml min^{-1} 1.73 m^{-2}) was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI 2009) equation for serum creatinine. All laboratories were certified and located on site of the participating clinics.

2.6 | Statistical analysis

The statistical analyses were performed with IBM SPSS Statistics Version 22.0 and R Statistical Software Version 3.6.1. Two-sided *P*-values ≤0.05 were considered statistically significant. All analyses were stratified for line of care (primary care/academic care) due to the oversampling of people treated in academic care.

Participant characteristics were summarized by polypharmacy level using descriptive statistics. Characteristics associated with polypharmacy were investigated with multinomial logistic regression. The level of polypharmacy was the outcome (no polypharmacy/moderate polypharmacy/severe polypharmacy) with no polypharmacy as the reference category. Characteristics potentially associated with polypharmacy were selected based on the literature and availability: age (per 10 years); sex (men/women); educational level (low/middle/high); white North European ethnicity (yes/no); smoking status (never/former/current); alcohol consumption (none/light–moderate/heavy); BMI (per 5 kg/m^2); SBP (per 20 mmHg); HbA_{1c} categories [< 54 mmol/mol (< 7.1%), 54–64 mmol/mol (7.1–8.0%), >64 mmol/mol (> 8.0%)]; diabetes duration (per 10 years); eGFR (per 20 ml min^{-1} 1.73 m^{-2}); LDL cholesterol (mmol/l) and prior CVD (yes/no). We first investigated the characteristics separately in univariable multinomial logistic regression models. Second, we included all characteristics to construct a multivariable association model. The results were presented as odds ratios (ORs) with corresponding 95% confidence intervals (CI).

In case of missing values for potential characteristics, we performed multiple imputation using the fully conditional specification method with 10 data sets and 20 iterations.[27] The maximum percentage imputed was 16% (diabetes duration) for primary care and 11% (CVD) for academic care. Moreover, we performed complete case analyses as sensitivity analyses.

3 | RESULTS

3.1 | Participant characteristics

The mean age was 63 years (SD 10) in primary care and 60 years (SD 11) in academic care (Table 1). At both lines of care, 40% of people with diabetes were women. The median number of concomitantly used medications was 5 (IQR 3–7) in primary care and 7 (IQR 5–10) in academic care. In primary care, the prevalence of moderate polypharmacy (5–9 medications) was 44% and the prevalence of severe polypharmacy (≥10 medications) was 10%. In academic care, the prevalence of moderate and severe polypharmacy were 53% and 29%, respectively.

3.2 | Characteristics associated with moderate polypharmacy and severe polypharmacy

The overall differences were small in the associations observed in the univariable (Table S1) and the multivariable models (Figure 1; Table S3). Results from the complete case analyses (Tables S2 and S4) were generally similar as the results from the analyses with imputed data, and the latter are used throughout.

3.3 | Sociodemographic characteristics and polypharmacy

At both lines of care, higher age was independently associated with a higher odds of both moderate and severe polypharmacy, compared with no polypharmacy (Figure 1). Being a woman was associated with a higher odds of moderate and severe polypharmacy in primary care, whereas having a white North European ethnicity was associated with a higher odds of severe polypharmacy in academic care only. A high educational level was associated with a lower odds of severe polypharmacy in both lines of care.

3.4 | Lifestyle characteristics and polypharmacy

Current smoking was associated with a higher odds of moderate and severe polypharmacy in both lines of care, whereas former smoking was associated with a higher odds of polypharmacy in academic care only (Figure 1). Being a light-to-moderate drinker was associated with a lower odds of moderate polypharmacy in academic care and with a lower odds of severe polypharmacy in both lines of care.

3.5 | Cardiometabolic characteristics and polypharmacy

A higher BMI and prior CVD were consistently associated with a higher odds of moderate and severe polypharmacy,

TABLE 1 Baseline characteristics of 6759 participants of the Diabetes Pearl cohort, according to medication categories: no polypharmacy, moderate polypharmacy and severe polypharmacy, and stratified by line of care

		Primary care			Academic care		
		N = 3886			*N* = 2873		
	Total *N* = 6759	**No polypharmacy (0–4)** *N* = 1788	**Moderate polypharmacy (5–9)** *N* = 1716	**Severe polypharmacy (≥ 10)** *N* = 382	**No polypharmacy (0–4)** *N* = 518	**Moderate polypharmacy (5–9)** *N* = 1513	**Severe polypharmacy (≥ 10)** *N* = 842
Age, years	62.0 ± 10.2	60.9 ± 9.6	65.0 ± 8.8	66.8 ± 9.1	53.6 ± 12.0	60.8 ± 10.1	62.9 ± 9.3
Women	40	37	42	45	43	38	42
Educational level							
Low	56	50	60	65	46	55	62
Middle	23	25	21	20	26	22	21
High	21	25	19	15	28	23	15
White North European ethnicity	88	96	95	95	71	77	82
Smoking status							
Current smokers	18	19	18	20	19	17	17
Former smokers	40	35	32	31	37	49	53
Never smokers	42	46	50	49	44	34	30
Alcohol consumption							
None	44	30	37	45	48	54	65
Light to moderate	47	59	52	44	46	38	29
Heavy	9	12	11	11	6	8	6
BMI, kg/m^2	30.7 ± 5.8	29.2 ± 4.7	30.3 ± 5.2	31.5 ± 5.9	30.1 ± 6.3	31.6 ± 6.3	33.4 ± 6.5
Systolic blood pressure, mmHg	142 ± 19	139 ± 18	142 ± 19	142 ± 22	139 ± 20	145 ± 19	144 ± 21
Diabetes duration, years	8 (3, 14)	4 (2, 8)	6 (3, 11)	7 (3, 11)	8 (3, 15)	13 (7, 19)	14 (8, 20)
HbA_{1c}, mmol/mol (%)	55 ± 14 (7.2 ± 1.3)	49 ± 11 (6.7 ± 1.0)	52 ± 11 (6.9 ± 1.0)	53 ± 11 (7.0 ± 1.0)	61 ± 16 (7.7 ± 1.5)	61 ± 15 (7.7 ± 1.4)	61 ± 15 (7.7 ± 1.4)
LDL cholesterol, mmol/l	2.4 ± 0.9	2.7 ± 1.0	2.3 ± 0.8	2.2 ± 0.8	2.8 ± 0.9	2.4 ± 0.9	2.3 ± 0.9

(Continues)

TABLE 1 (Continued)

		Primary care			Academic care		
		N = 3886			*N* = 2873		
	Total *N* = 6759	**No polypharmacy (0–4)** *N* = 1788	**Moderate polypharmacy (5–9)** *N* = 1716	**Severe polypharmacy (≥ 10)** *N* = 382	**No polypharmacy (0–4)** *N* = 518	**Moderate polypharmacy (5–9)** *N* = 1513	**Severe polypharmacy (≥ 10)** *N* = 842
eGFR, ml min^{-1} 1.73 m^{-2}	81.7 ± 21.1	85.4 ± 16.0	80.1 ± 17.2	73.1 ± 22.3	95.0 ± 21.6	81.9 ± 23.1	72.4 ± 26.1
Prior CVD	37	13	36	59	14	40	60
CVD status missing	10	8	10	12	14	11	10
Insulin use	40	10	24	36	54	69	80
Medication (*N*)							
Glucose-lowering	2 (1, 2)	1 (0, 1)	2 (1, 2)	2 (1, 2)	2(1, 2)	2 (2, 3)	2 (2, 3)
Cardiovascular	3 (1, 4)	1 (0, 2)	4 (2, 4)	6 (4, 7)	1 (0, 2)	3 (2, 5)	5 (4, 7)
Other[a]	1 (0, 3)	0 (0, 1)	1 (0, 2)	4 (3, 6)	0 (0, 1)	1 (0, 2)	5 (3, 7)

Note: Values are percentages, except means ± SD or medians (IQR).

Abbreviations: BMI = body mass index; CVD = cardiovascular disease; eGFR = estimated Glomerular Filtration Rate; HbA1c = glycated haemoglobin; LDL = low-density lipoprotein; N = number.

[a]Other medication indicates non-glucose lowering and non-cardiovascular medication.

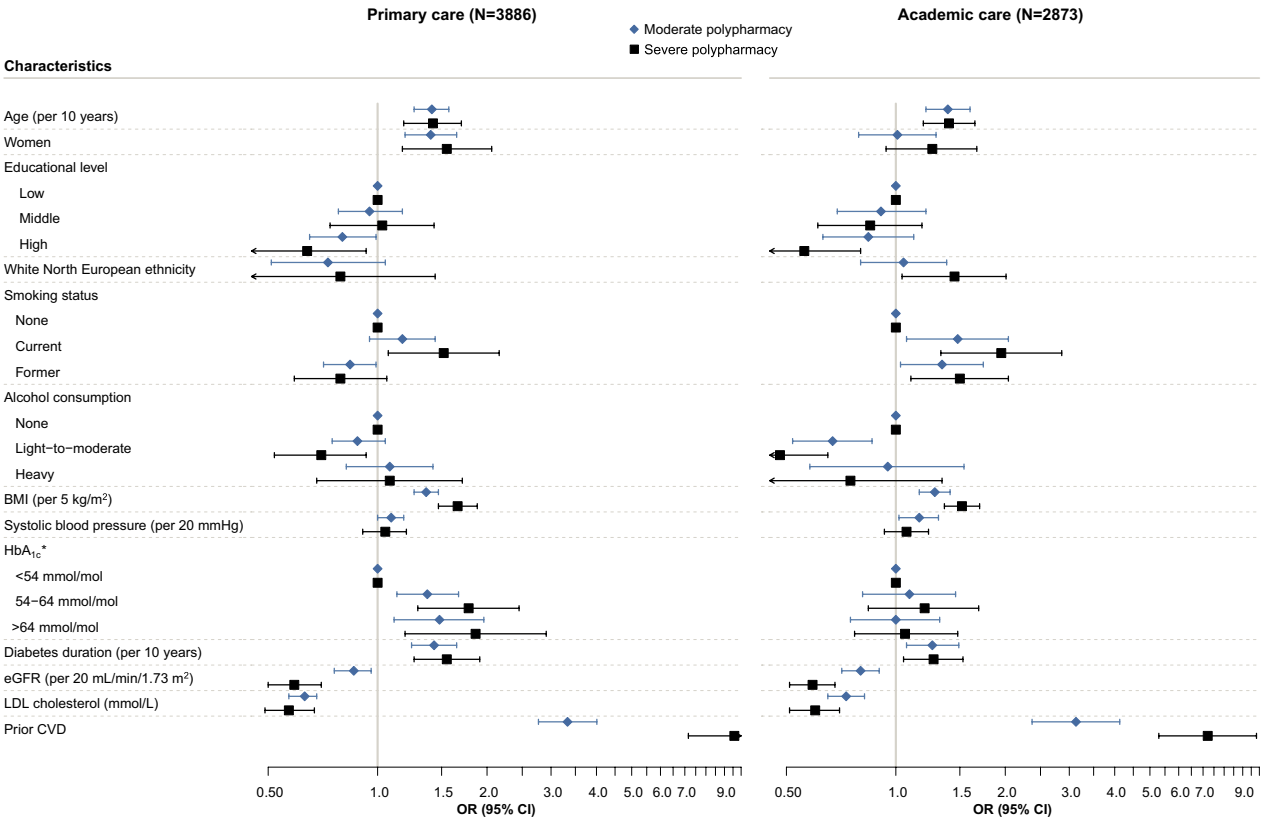

FIGURE 1 Multivariable association models of sociodemographic, lifestyle and cardiometabolic characteristics with level of polypharmacy in 6759 people of the Diabetes Pearl cohort, stratified by line of care. No polypharmacy was the reference category in both analyses. The results are presented as adjusted odds ratios (ORs) with 95% confidence intervals (95% CI) of the multivariable multinomial logistic regression analysis with imputed data. Refer to Table S3 for the exact numbers. *HbA_{1c} categories: <54 mmol/mol (< 7.1%), 54–64 mmol/mol (7.1–8.0%), >64 mmol/mol (> 8.0%). CVD, cardiovascular disease

whereas higher LDL cholesterol and eGFR levels were associated with a lower odds of moderate and severe polypharmacy, in both lines of care (Figure 1). A higher HbA_{1c} was associated with a higher odds of moderate and severe polypharmacy in primary care only.

3.6 | Medication characteristics

The most prevalent medication subgroups in our cohort of people with type 2 diabetes were: (1) A10 drugs used in diabetes (76% in primary care and 97% in academic care), i.e. glucose-lowering medication; (2) C10 lipid-modifying agents (69% in primary care and 76% in academic care); and (3) C09 agents acting on the renin–angiotensin system (50% in primary care and 71% in academic care) (Figure 2).

At both lines of care and levels of polypharmacy, a large amount of the medication consisted of glucose-lowering and cardiovascular medications (Table 1). Furthermore, in the moderate and severe polypharmacy groups a larger part of the medication consisted of 'other' medication – a heterogeneous group of many medication subgroups (Figure 2) – of which were most prevalently used: (1) A02 drugs for acid-related disorders (in 24% of the people in primary care and 38% in academic care); and (2) R03 drugs for obstructive airway diseases (10% in primary care and 12% in academic care).

4 | DISCUSSION

A major finding of our study is that moderate and severe polypharmacy exist in over half of the people with type 2 diabetes in primary care, and even more pronounced in academic care. We observed that people with polypharmacy across both lines of care generally are older, less educated, and have an unhealthier lifestyle and a poorer cardiometabolic health. Furthermore, people with severe polypharmacy were characterized by a relatively high use of non-diabetes and non-cardiovascular medications. These results highlight the significance of polypharmacy in type 2 diabetes.

Our prevalence estimates of moderate and severe polypharmacy are similar to previous studies in type 2 diabetes populations. Studies performed in secondary or tertiary care settings reported a total polypharmacy prevalence varying from 57% to

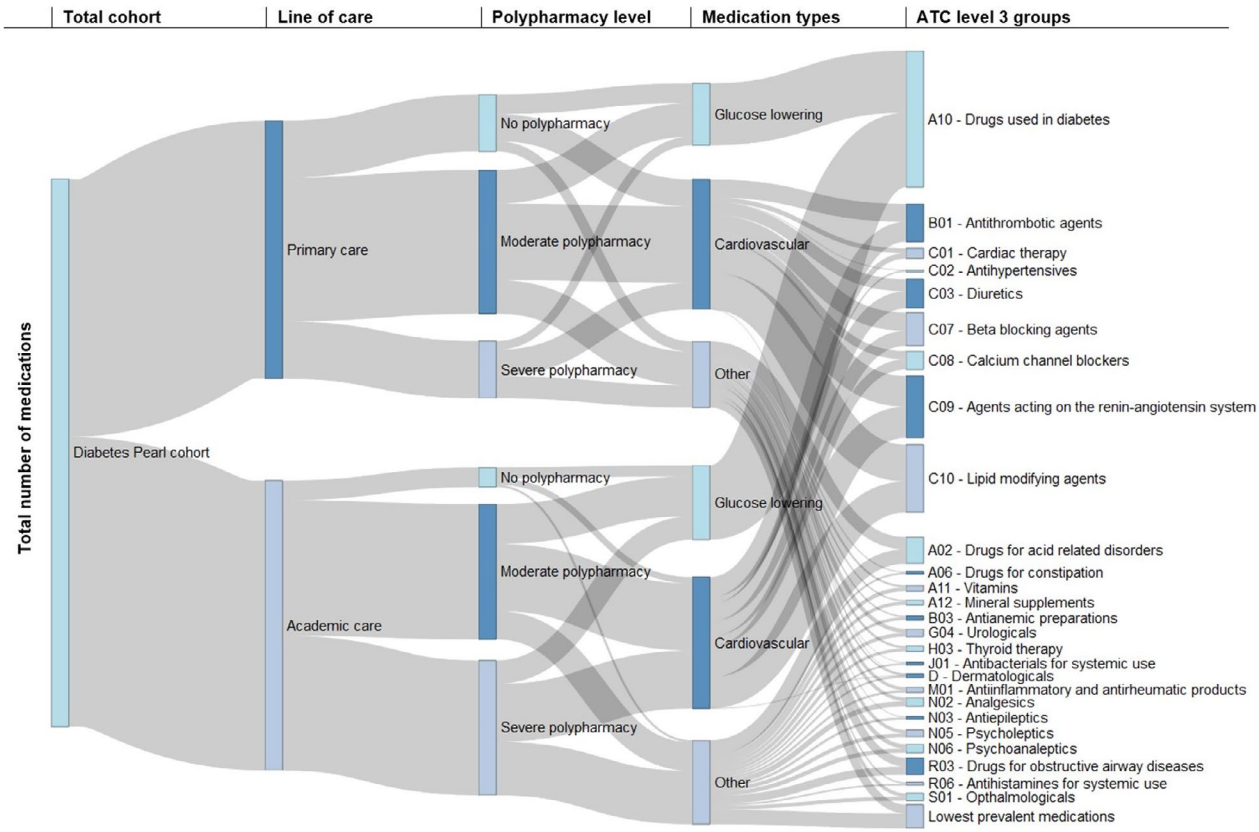

FIGURE 2 Overview of the total number of medications used in the Diabetes Pearl cohort, stratified by line of care, polypharmacy level, main medication types and level 3 ATC codes. No polypharmacy, 0–4 medications; moderate polypharmacy, 5–9 medications; severe polypharmacy, ≥10 medications). ATC, Anatomical Therapeutic Chemical classification

89%,[2,5–7] compared with 82% in our academic care cohort. The total polypharmacy prevalence of 54% in our primary care cohort was lower than previously reported in a primary care setting (72%),[9] but similar to a general population cohort (57%).[7]

The majority of the participant characteristics we identified were consistent with the literature, including higher age,[1,7,8] women,[1,6] low educational level,[7] higher BMI,[6] longer diabetes duration[6,8] and prior CVD.[1,6] We also identified novel characteristics of polypharmacy: light-to-moderate alcohol consumption, higher LDL cholesterol and higher eGFR associated with a lower odds, and current smoking associated with a higher odds of polypharmacy. Our finding that higher LDL cholesterol was associated with a lower polypharmacy odds is based on the analysis of treated and untreated LDL values: lipid-lowering medication contributed to low LDL cholesterol as well as ending up in the polypharmacy group. Higher HbA_{1c} level was only associated with a higher polypharmacy odds in primary care and white North European ethnicity only in academic care. The latter can probably be explained by the fact that almost all participants in our primary care cohort had a white North European ethnicity, which is merely a reflection of the underlying geographical areas in the Netherlands.

Alongside the prevalence and participant characteristics, we assessed which medication subtypes were often used in people with type 2 diabetes in relation to polypharmacy. It was not surprising that virtually all participants in our study used large numbers of glucose-lowering and cardiovascular medication, because the treatment of type 2 diabetes often requires the prescription of glucose-lowering medication, lipid-lowering medication and angiotensin-converting enzyme inhibitors. The largest difference in medication use between polypharmacy levels was observed in the 'other' medication group (i.e. non glucose-lowering and non-cardiovascular), which was especially frequently used in people with severe polypharmacy. This is thought to be due to high levels of comorbidity among people with type 2 diabetes, such as depression, anxiety, pulmonary disease and arthritis.[3,9,28] The most prevalently used 'other' medications in our study population also reflect these common comorbidities (Figure 2).

Although it is not possible to identify cause and effect due to our cross-sectional study design, we suspect that the people with polypharmacy have more severe diabetes and more diabetes-related comorbidities.[3,9,28] Another contributing factor might be that certain medications that are sometimes used in people with type 2 diabetes due to comorbidities, such

as antidepressants, antipsychotics and beta-blocking medication, have shown to increase weight as adverse effect.[29] Furthermore, it is possible that people with polypharmacy might not take their prescribed medication,[30] although taking glucose-lowering and cardiovascular medication is necessary to maintain adequate cardiometabolic control.

Our findings that people with worse controlled diabetes and more diabetes complications are being prescribed more medications might be obvious for researchers and clinicians. However, they highlight how complex polypharmacy is in the treatment and management of type 2 diabetes. Although often regarded as a negative feature, this study cannot judge whether polypharmacy was good or bad in this group of people with diabetes. It may well be that polypharmacy is partly inevitable in people with complicated diabetes and the price of the often-associated multimorbidity.

Nevertheless, as polypharmacy is very common among people with type 2 diabetes in all lines of care, it is essential that this high number of medications regularly receives attention in the physician–patient consultation. Performing a regular medication review is probably very important in the treatment of people with type 2 diabetes. Although it is often not possible to reduce the number of medications if all have been prescribed according to the guidelines, it is essential to detect potential interactions and adverse reactions. Moreover, it is important to pay special attention to whether the prescribed medication is taken in people with type 2 diabetes and polypharmacy.

4.1 | Strengths and limitations

Our study had several strengths. The large study population had high geographical coverage of the Netherlands and included people from all types of care. Moreover, we had access to comprehensive measures of sociodemographic, cardiometabolic and lifestyle characteristics, as well as medication characteristics, all collected via standard operating procedures.

A limitation of this study was its cross-sectional design. Therefore, it was not possible to infer causality for the observed associations. In addition, some covariates had missing data, but the differences between the complete case analyses and the analyses with imputed data were small. Therefore, we think it is unlikely that missing data affected our conclusions. Furthermore, as we investigated many characteristics in our study, this probably inflated the probability of chance findings. Finally, the odds ratios presented in this study cannot be interpreted as relative risks, because the prevalence of the outcomes (moderate and severe polypharmacy) was high.[31]

In summary, severe and moderate polypharmacy are prevalent in over half of the people with type 2 diabetes in primary care and even more in academic care. People with polypharmacy are characterized by poorer cardiometabolic status. These results highlight the significance of polypharmacy in type 2 diabetes.

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COMPETING INTERESTS

None declared.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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