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Metabolically "extremely unhealthy" obese and non-obese people with diabetes and the risk of cardiovascular adverse events: the Silesia Diabetes - Heart Project

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Abstract

Background There is a growing burden of non-obese people with diabetes mellitus (DM). However, their cardiovascular risk (CV), especially in the presence of cardiovascular-kidney-metabolic (CKM) comorbidities is poorly characterised. The aim of this study was to analyse the risk of major CV adverse events in people with DM according to the presence of obesity and comorbidities (hypertension, chronic kidney disease, and dyslipidaemia).

Methods We analysed persons who were enrolled in the prospective Silesia Diabetes Heart Project (NCT05626413). Individuals were divided into 6 categories according to the presence of different clinical risk factors (obesity and CKM comorbidities): (i) Group 1: non-obese with 0 CKM comorbidities; (ii) Group 2: non-obese with 1–2 CKM comorbidities; (iii) Group 3: non-obese with 3 CKM comorbidities (non-obese "extremely unhealthy"); (iv) Group 4: obese with 0 CKM comorbidities; (v) Group 5: obese with 1–2 CKM comorbidities; and (vi) Group 6: obese with 3 CKM comorbidities (obese "extremely unhealthy"). The primary outcome was a composite of CV death, myocardial infarction (MI), new onset of heart failure (HF), and ischemic stroke.

Results 2105 people with DM were included [median age 60 (IQR 45–70), 48.8% females]. Both Group 1 and Group 6 were associated with a higher risk of events of the primary composite outcome (aHR 4.50, 95% CI 1.20-16.88; and aHR 3.78, 95% CI 1.06–13.47, respectively). On interaction analysis, in "extremely unhealthy" persons the impact of CKM comorbidities in determining the risk of adverse events was consistent in obese and non-obese ones (P_{int}=0.824), but more pronounced in individuals aged < 65 years compared to older adults (P_{int}= 0.028).

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Conclusion Both non-obese and obese people with DM and 3 associated CKM comorbidities represent an "extremely unhealthy" phenotype which are at the highest risk of CV adverse events. These results highlight the importance of risk stratification of people with DM for risk factor management utilising an interdisciplinary approach.

Keywords Diabetes mellitus, Metabolically unhealthy, Comorbidities, Obesity, Cardiovascular events

Introduction

Diabetes mellitus (DM) is an important public health challenge associated with a high risk of mortality and morbidity from cardiovascular (CV) diseases [1, 2]. Overweight and obesity are significant risk factors for the development of DM, as they are associated with insulin resistance that, in turn, favours inflammation and accelerated loss of pancreatic β-cell function [3]. Moreover, other comorbidities, like hypertension, dyslipidaemia, and chronic kidney disease (CKD), often coexist. They constitute the cardiovascular-kidney-metabolic (CKM) axis of comorbidities and complicate the clinical course of these persons, heightening the risk of CV events [4].

In clinical practice, the holistic management of people with type 2 DM, who are often living with overweight or obesity, should be aimed at reducing the risk of diabetes-related complications. This approach includes (apart from lifestyle modifications and education) multiple, evidence-based interventions such as management of weight, glycaemia, blood pressure and lipids along with using medications with cardiovascular and kidney outcomes benefits [5–7].

Nevertheless, the prevalence of people with DM without obesity is about 20% and has been increasing in recent decades [8]. Results from a US survey showed that between 2015 and 2020 DM increased by 17.8% among "lean" [defined as body mass index (BMI) of <25 kg/m^2] adults, while no significant changes among overweight and obese adults were observed [9]. Similarly, a recent meta-analysis on temporal trends of DM incidence showed a continuous growth among normal-weight persons since 1985, with an estimated increase of 36% every 5 years [10].

Although obese and "lean"/normal-weight people with DM have some differences in terms of aetiology and pathophysiology, the metabolically obese normal weight (MONW) phenotype, a term used to describe individuals who present obesity alterations (e.g. reduced insulin sensitivity, hypertension, DM, and hypertriglyceridemia), despite having normal weight, present a higher risk of adverse outcomes compared to people without DM [11, 12]. This relative contribution of obesity requires further elucidation over the presence of other CV risk factors in determining the risk of adverse events in people with DM [13–16].

The aim of this study was to assess the risk of CV events in DM based on the presence or absence of obesity and stratified by CKM comorbidities.

Methods

Study design

The design of the Silesia Diabetes-Heart Project has been previously reported [17]. Briefly, the Silesia - Heart Project is a single centre, observational, prospective registry where people with diabetes, hospitalized in the Diabetology Ward in Zabrze and from the Outpatient Diabetology Clinics in the Silesia Region, Poland between January 2015 and March 2023, were enrolled. Adult persons between age 18 years and 85 years with type 1 DM or type 2 DM who provided written informed consent were enrolled in the registry. The study protocol was approved by the local Ethics Committee, and the study was conducted in accordance with the Good Clinical Practice and the Declaration of Helsinki. The study is registered on ClinicalTrials.gov (NCT05626413).

At baseline, data concerning demographics, and medical history for hospitalized persons were collected. Moreover, we reported information concerning glucose - lowering treatments [i.e. insulin, metformin, dipeptidyl peptidase 4 (DPP4) inhibitors, glucagon-like peptide-1 receptor agonists (GLP-1 RA), sodium-glucose co-transporter 2 (SGLT2) inhibitors, and combination therapy with insulin and oral glucose-lowering drugs], antiplatelet (APT) therapy, oral anticoagulants (OAC), the most used cardiovascular drugs [i.e. beta-blockers, angiotensin converting enzyme inhibitors (ACEi), angiotensin receptor blockers (ARB), calcium-channel blockers, statins] and non-cardiovascular drugs (i.e. xanthine oxidase inhibitors).

For the purpose of this analysis, we included people with complete data about the obesity status, hypertension, dyslipidaemia, and CKD, defined according to the current guidelines [18–22]. Obesity was defined as a BMI of 30 kg/m² or greater. Hypertension, dyslipidaemia, and CKD were considered CKM comorbidities. CKD was defined as an estimated glomerular filtration rate (eGFR) of less than 60 ml/min/1.73 m² or a urine albumin-to-creatinine ratio equal or greater than 30 mg/g lasting for more than 3 months [23]. Including CKD among the CKM comorbidities allowed for a comprehensive evaluation of cardiovascular risk [24, 25]. Hypertension was defined as a systolic blood pressure of 140 mm Hg or higher, or a diastolic blood pressure of 90 mm Hg or higher, or the use of antihypertensive medication [20]. Dyslipidaemia encompassed both hypercholesterolemia and hypertriglyceridemia as defined previously [26].

Definition of clinical risk groups

People were divided into 6 categories of clinical CV risk based on the presence of obesity and the number of CKM comorbidities, as follows:

- Group 1: non-obese with 0 CKM comorbidities;
- Group 2: non-obese with 1–2 CKM comorbidities;
- Group 3: non-obese with 3 CKM comorbidities;
- Group 4: obese with 0 CKM comorbidities;
- Group 5: obese with 1–2 CKM comorbidities;
- Group 6: obese with 3 CKM comorbidities.

Both non-obese and obese people with DM and 3 additional CKM comorbidities were defined as metabolically "extremely unhealthy" groups.

Follow-up and adverse events

Follow-up information was collected through personal visits or phone contact with the person or the person's family member between March 2021 and November 2023.

In this analysis, the primary outcome was defined as a composite of CV death, myocardial infarction (MI), new onset of heart failure (HF), and ischemic stroke.

Statistical analysis

Continuous variables are reported as mean and standard deviation (SD) or median and interquartile range [IQR] and compared with appropriate parametric and non-parametric tests. Categorical variables are shown as frequencies and percentages and compared using the 2-test. For all the analyses, group 1 was used as the reference one.

Multivariable logistic regression was used to assess the associations between clinical risk groups and the use of various pharmacological treatments: insulin, metformin, sulfonylureas, GLP1 RA, SGLT2 inhibitors, DPP4 inhibitors, insulin with oral glucose-lowering drugs, APT, and OAC drugs. These analyses were adjusted for age, sex, type of DM, duration of DM, current smoking, and previous coronary artery disease (CAD), considered as covariates, or independent variables. Results are reported as Odds Ratio (OR) and 95% Confidence Intervals (CI).

The incidence rate (IR) of adverse outcomes was calculated as the number of events / total person-years ratio and reported as incidence for 1000 persons/year with the relative 95% CI. Kaplan-Meier survival curves were used to illustrate the differences in the survival distributions and these differences were statistically tested by the Log-Rank test. Cox regression models were used to evaluate the association between the different groups and the risk of the composite outcome. Group 1 was used as the reference. Results are shown as Hazard Ratio (HR), adjusted Hazard Ratio (aHR) and 95% CI.

For Cox regression models, we built 2 models: Model 1, adjusted for age and sex; and Model 2, adjusted for age, sex, duration of DM, current smoking, and previous CAD. Additionally, we divided the population into two groups, the "extremely unhealthy" group and the "non-extremely unhealthy" group. We performed an interaction analysis to assess if the association between the groups and the risk of primary outcome was modified by different sub-groups with the relevant clinical characteristics (age < or ≥ 65 years, males or females, obese or non-obese, type 1 or type 2 DM). All the interaction analyses were adjusted for the same variables included in the Cox regression Model 2. A two-sided $p < 0.05$ was considered statistically significant. All the analyses were performed using the SPSS statistical software version 29.0.2.0 (SPSS, Inc., Chicago, IL, USA) or using R (version 4.3.2).

Results

From the 3056 persons originally enrolled in the Silesia Diabetes-Heart Project registry, 2105 (68.8%) persons [median age (IQR), 60 (45–70) years; 48.8% females] had complete clinical and follow-up information and were included in this analysis (Fig. 1). Among these persons, 1066 (50.6%) were non-obese and 1039 (49.4%) were obese. The majority had at least 1 CKM comorbidity [1736 (82.5%) in the whole cohort].

Baseline characteristics of the different clinical risk groups are summarised in Table 2. Group 1 (non-obese with 0 CKM comorbidities) consisted of the youngest persons [median age, 27 (22-37)], with a shorter duration of the disease [median years, 7 (1-12)], and a high prevalence of type 1 DM (82.1%). Overall, among people without obesity (Groups 1–3), an increase in the number of comorbidities correlated with older age. Similarly, the duration of the disease progressively increased, while the prevalence of people with type 1 DM became lower. Table 1, summarizes achieving guideline-recommended targets for the examined groups of people. Analogous findings were observed in obese people (Groups 4–6), with a gradual rise in median age and duration of DM as the number of comorbidities increased.

Extremely unhealthy people with 3 CKM comorbidities exhibited a higher prevalence of previous CV disease compared to those with 0 or 1–2 comorbidities in both obese and non-obese persons. Among "extremely unhealthy" persons, those in the obese category (Group 6) demonstrated significantly higher absolute rates of CAD (58.8% vs. 43.3%, $p < 0.001$) and history of HF (36.5% vs. 23.1%, $p < 0.001$) compared to their non-obese counterparts (Group 3).

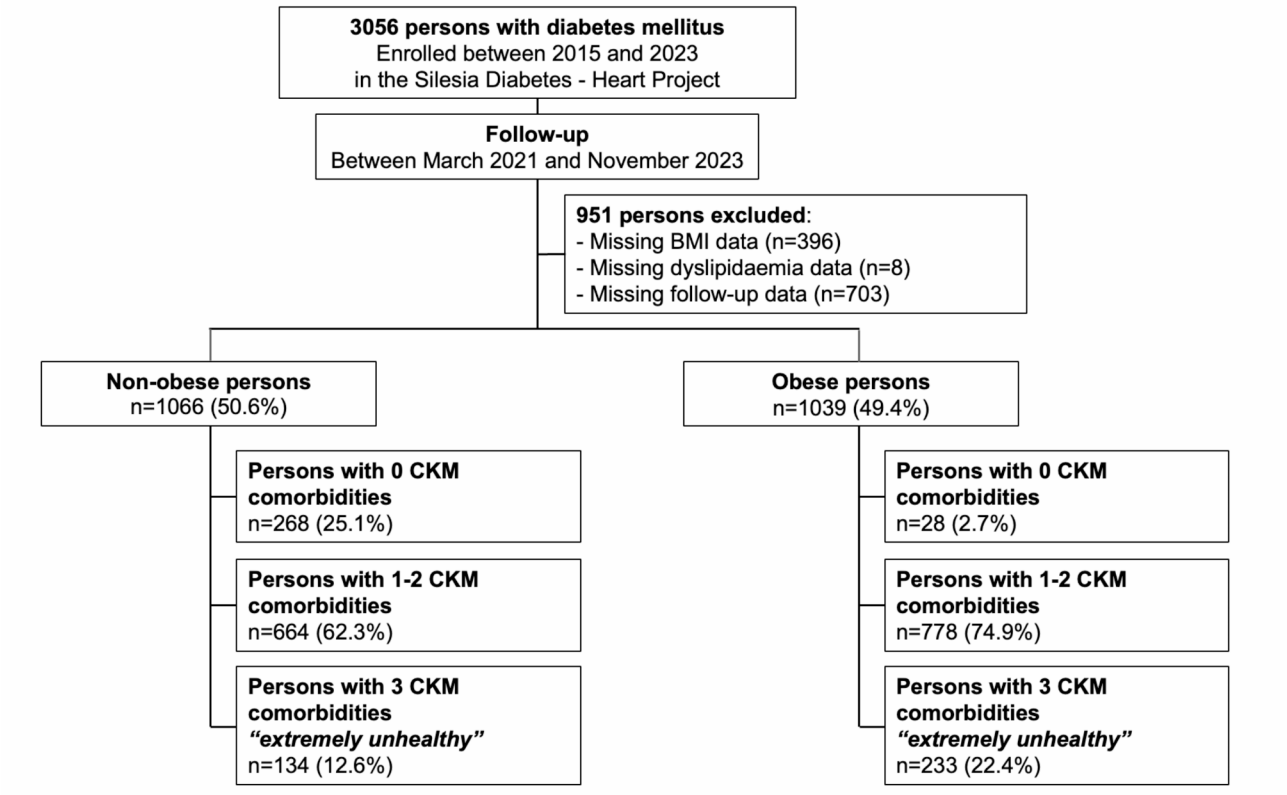

Fig. 1 Flowchart of the study. BMI, body mass index; CKM cardiovascular-kidney-metabolic

Treatments

Treatments received by the different groups are reported in Table 3, and the results of multivariable logistic regression analysis are summarised in Table 4.

Insulin was frequently used in Group 1 (94%) and Group 6 (87.1%); however, multivariable logistic regression analysis showed no differences among the groups. SGLT2 inhibitors were more likely prescribed to people with 1–2 CKM comorbidities, both non-obese (Group 2: 15.7%) and obese (Group 5: 29.8%), as confirmed by regression analysis after adjustment for confounders (OR 2.94, 95% CI 1.20–7.23; and OR 4.16, 95% CI 1.71–10.11, respectively).

Obese people with 1–2 or 3 CKM comorbidities showed the highest use of GLP1 RA (6.7% and 5.6%, respectively). This finding was confirmed by multivariable analysis, which revealed that compared to non-obese people with 0 CKM comorbidities, they had almost 8-fold increased odds of receiving this treatment (OR 7.40, 95% CI 1.57–34.81; and OR 8.16, 95% CI 1.53–43.52, respectively).

When considering insulin combined with oral glucose-lowering drugs, the highest prescription prevalence was observed in the obese groups (ranging from 42.9% in Group 4 to 64.7% in Group 6). However, after multivariable logistic analysis, all groups showed higher use of combined treatment compared to non-obese people with 0 comorbidities, except for non-obese with 3 comorbidities and obese with 0 CKM comorbidities.

In terms of antithrombotic therapy, antiplatelet medications were more likely used in non-obese and obese people with at least 1 CKM comorbidity, with the greatest prevalence reported in non-obese and obese "extremely unhealthy" persons (69.4% and 69.1%). These results were confirmed by multivariable logistic regression. OAC use was the highest in obese people with 3 CKM comorbidities (18.9%), but no significant differences were observed after adjusting for confounding factors.

Risk of adverse events

During a median follow-up of 987 (622–1437) days, a total of 152 (7.2%) events of the primary composite outcome occurred. Compared to non-obese people with 0 CKM comorbidities (Group 1) (IR per 1000 persons-years: 7.21, 95% CI 2.34–16.83), those with at least 1 CKM comorbidity had significantly higher IRs for the composite outcome, with the highest rates for non-obese and obese people with 3 CKM comorbidities (IR 50.26, 95% CI 30.26–78.49; and IR 40.35, 95% CI 26.81–58.32, respectively), as shown in Table 5. Kaplan-Meier curves illustrating the primary composite outcome for different groups are depicted in Fig. 2. At multivariable Cox

Table 1 Baseline characteristics according to clinical risk groups

	Non-obese 0 CKM com.	Non-obese 1–2 CKM com.	Non-obese 3 CKM com.	Obese 0 CKM com.	Obese 1–2 CKM com.	Obese 3 CKM com.	*p*-value
	Group 1	Group 2	Group 3	Group 4	Group 5	Group 6	
Total, n (%)	268 (12.7)	664 (31.5)	134 (6.4)	28 (1.3)	778 (37)	233 (11.1)	
Males, n (%)	137 (51.1)	321 (48.3)	82 (61.2)	18 (64.3)	381 (49)	139 (59.7)	0.003
Age (years), median [IQR]	27 [22–37]	57 [43–69]	72 [62–80]	51 [36–66]	62 [54–69]	69 [63–75]	< 0.001
DM type 1, n (%)	220 (82.1)	228 (34.2)	16 (11.9)	8 (28.6)	48 (6.2)	4 (1.7)	< 0.001
Duration of diabetes (years), median [IQR]	7 [1–12]	10 [3–16]	12 [9–20]	5 [1–11]	10 [5–15]	12 [10–20]	< 0.001
Emergency admission, n (%)	94 (35.1)	249 (37.5)	56 (41.8)	11 (39.3)	202 (26)	61 (26.2)	< 0.001
Diabetes decompensation reason for admission, n (%)	171 (63.8)	425 (64)	88 (65.7)	15 (53.6)	526 (67.6)	162 (69.5)	0.321
Obesity, n (%)	0 (0)	0 (0)	0 (0)	28 (100)	778 (100)	233 (100)	< 0.001
BMI (kg/m^2), median [IQR]	22 [20–25]	25 [23–28]	27 [24–28]	33 [31–37]	34 [32–38]	35 [32–39]	< 0.001
Hypertension, n (%)	0 (0)	420 (63.3)	134 (100)	0 (0)	695 (89.3)	233 (100)	< 0.001
Systolic BP (mmHg), mean (SD)	118 (10)	126 (13)	133 (16)	124 (9)	133 (14)	133 (15)	< 0.001
Diastolic BP (mmHg), mean (SD)	74 (7)	76 (7)	76 (8)	76 (6)	78 (7)	77 (8)	< 0.001
Dyslipidemia, n (%)	0 (0)	401 (60.4)	134 (100)	0 (0)	567 (73.2)	233 (100)	< 0.001
CKD, n (%)	0 (0)	81 (12.2)	134 (100)	0 (0)	67 (8.6)	233 (100)	< 0.001
Current smoker, n (%)	54 (20.1)	154 (23.2)	21 (15.7)	3 (10.7)	159 (20.4)	35 (15)	0.053
Hyperuricaemia, n (%)	5 (1.9)	111 (16.7)	80 (59.7)	5 (17.9)	266 (34.2)	164 (70.4)	< 0.001
Diabetic retinopathy, n (%)	49 (18.3)	223 (33.6)	45 (33.6)	8 (28.6)	241 (31)	94 (40.3)	< 0.001
Generalized atherosclerosis, n (%)	10 (3.7)	229 (34.5)	87 (64.9)	8 (28.6)	271 (34.8)	147 (63.1)	< 0.001
Venous insufficiency, n (%)	1 (0.4)	41 (6.2)	19 (14.2)	4 (14.3)	100 (12.9)	45 (19.3)	< 0.001
Diabetic peripheral neuropathy, n (%)	9 (3.4)	78 (11.7)	13 (9.7)	3 (10.7)	50 (6.4)	21 (9)	< 0.001
Diabetic foot, n (%)	3 (1.1)	21 (3.2)	9 (6.7)	2 (7.1)	15 (1.9)	8 (3.4)	0.009
MASLD, n (%)	35 (13.1)	250 (37.7)	65 (48.5)	14 (50)	560 (72)	173 (74.2)	< 0.001
CAD, n (%)	3 (1.1)	142 (21.4)	58 (43.3)	4 (14.3)	261 (33.5)	137 (58.8)	< 0.001
Heart failure, n (%)	2 (0.7)	73 (11)	31 (23.1)	3 (10.7)	133 (17.1)	85 (36.5)	< 0.001
AF, n (%)	2 (0.8)	38 (5.8)	15 (11.5)	2 (7.1)	62 (8.2)	34 (15)	< 0.001
Previous stroke, n (%)	0 (0)	35 (5.3)	28 (20.9)	1 (3.6)	49 (6.3)	31 (13.3)	< 0.001
Degenerative disease of the spine, n (%)	17 (6.3)	230 (34.6)	55 (41)	8 (28.6)	343 (44.1)	118 (50.6)	< 0.001
Carotid artery disease, n (%)	0 (0)	11 (1.7)	4 (3)	0 (0)	10 (1.3)	7 (3)	0.066
PAD, n (%)	1 (0.4)	26 (3.9)	6 (4.5)	2 (7.1)	29 (3.7)	17 (7.3)	0.004
Total cholesterol (mmol/l), median [IQR]	4.10 [3.48–4.52]	4.94 [3.92–5.64]	4.49 [3.60–5.40]	4.39 [3.27–4.63]	4.53 [3.72–5.51]	4.28 [3.53–5.07]	< 0.001
LDL cholesterol (mmol/l), median [IQR]	2.07 [1.75–2.42]	2.49 [1.82–3.27]	2.06 [1.59–2.87]	2.43 [1.72–2.76]	2.30 [1.58–3.16]	2.04 [1.53–2.61]	< 0.001
HDL cholesterol (mmol/l), median [IQR]	1.48 [1.24–1.79]	1.42 [1.10–1.85]	1.19 [0.97–1.54]	1.27 [1.11–1.62]	1.18 [0.97–1.41]	1.09 [0.92–1.28]	< 0.001
Triglycerides (mmol/l), median [IQR]	0.87 [0.64–1.18]	1.27 [0.88–1.87]	1.53 [1.17, 2.26]	1.17 [0.81–1.53]	1.73 [1.23–2.59]	1.98 [1.47–2.66]	< 0.001
HbA1c (%), median [IQR]	8.50 [7.38–10.85]	8.82 [7.52–10.63]	8.40 [6.98–10.50]	7.70 [5.84–10.50]	9.05 [7.81–10.30]	8.70 [7.60-10.41]	0.203
eGFR (ml/min), median [IQR]	104.92 [91.46–119.80]	86.13 [70.56-106.15]	44.11 [35.08–53.09]	94.42 [73.29-108.87]	82.60 [69.67–97.92]	45.39 [35.16–54.13]	< 0.001

AF, atrial fibrillation; BMI, body mass index; BP, blood pressure; CAD, coronary artery disease; CKD, chronic kidney disease; CKM com., cardiovascular-kidney-metabolic comorbidities; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; HbA1c, glycated haemoglobin; HDL, high density lipoprotein; IQR, interquartile range; LDL, low density lipoprotein; MASLD, metabolic dysfunction-associated steatotic liver disease; PAD, peripheral artery disease; SD, standard deviation

Table 2 The percentage of persons achieving guideline-recommended target

Guideline-recommended target	Total	Non-obese 0 CKM com.	Non-obese 1–2 CKM com.	Non-obese 3 CKM com.	Obese 0 CKM com.	Obese 1–2 CKM com.	Obese 3 CKM com.
		Group 1	Group 2	Group 3	Group 4	Group 5	Group 6
LDL-C < 70 mg/dL	29.9	22.7	33.5	34.0	25.1	26.7	35.2
HbA1C < 7%	16.0	34.4	13.3	14.5	16.9	16.4	25.2
SBP < 140mmHg and DBP < 90mmHg	76.9	100	69.0	69.9	100	78.9	67.5
SBP < 130mmHg and DBP < 80mmHg	39.0	44.1	26.9	30.6	67.5	43.3	28.5

Results are expressed as percentage of persons achieving recommended targets

CKM com., cardiovascular-kidney-metabolic comorbidities; DBP, diastolic blood pressure; HbA1c, glyclated hemoglobin A1c; LDL-C, low density lipoprotein cholesterol; SBP, systolic blood pressure

Table 3 Treatments according to clinical risk groups

Number (%)	Non-obese 0 CKM com.	Non-obese 1–2 CKM com.	Non-obese 3 CKM com.	Obese 0 CKM com.	Obese 1–2 CKM com.	Obese 3 CKM com.	*p*-value
	Group 1	Group 2	Group 3	Group 4	Group 5	Group 6	
Insulin	252 (94)	511 (77)	92 (68.7)	19 (67.9)	588 (75.6)	203 (87.1)	< 0.001
Metformin	21 (7.8)	274 (41.3)	55 (41)	15 (53.6)	607 (78)	104 (44.6)	< 0.001
Sulfonylureas	30 (11.2)	171 (25.8)	45 (33.6)	5 (17.9)	175 (22.5)	51 (21.9)	< 0.001
SGLT2 inhibitors	6 (2.2)	104 (15.7)	13 (9.7)	2 (7.1)	232 (29.8)	24 (10.3)	< 0.001
GLP-1 receptor agonists	2 (0.7)	14 (2.1)	4 (3)	1 (3.6)	52 (6.7)	13 (5.6)	< 0.001
DPP4 inhibitors	25 (9.3)	83 (12.5)	20 (14.9)	4 (14.3)	101 (13)	43 (18.5)	0.079
Insulin with oral glucose- lowering drugs	47 (17.5)	262 (39.5)	52 (38.8)	12 (42.9)	503 (64.7)	131 (56.2)	< 0.001
ACEi or ARB	4 (1.5)	342 (51.5)	71 (53)	6 (21.4)	592 (76.1)	131 (56.2)	< 0.001
APT	6 (2.2)	247 (37.2)	93 (69.4)	4 (14.3)	429 (55.1)	161 (69.1)	< 0.001
OAC	2 (0.7)	45 (6.8)	20 (14.9)	3 (10.7)	84 (10.8)	44 (18.9)	< 0.001
Beta-blockers	7 (2.6)	288 (43.4)	105 (78.4)	5 (17.9)	490 (63)	191 (82)	< 0.001
Alpha-blockers	1 (0.4)	37 (5.6)	26 (19.4)	0 (0)	98 (12.6)	61 (26.2)	< 0.001
Calcium channel blockers	2 (0.7)	120 (18.1)	73 (54.5)	0 (0)	270 (34.7)	135 (57.9)	< 0.001
Loop diuretics	2 (0.7)	92 (13.9)	68 (50.7)	3 (10.7)	229 (29.4)	170 (73)	< 0.001
Non-loop diuretics	1 (0.4)	82 (12.3)	19 (14.2)	3 (10.7)	195 (25.1)	22 (9.4)	< 0.001
MRA	2 (0.7)	40 (6)	19 (14.2)	2 (7.1)	84 (10.8)	39 (16.7)	< 0.001
Statin	0 (0)	305 (45.9)	110 (82.1)	0 (0)	497 (63.9)	204 (87.6)	< 0.001
Fibrate	0 (0)	8 (1.2)	2 (1.5)	0 (0)	17 (2.2)	13 (5.6)	< 0.001
Allopurinol	1 (0.4)	69 (10.4)	59 (44)	2 (7.1)	199 (25.6)	139 (59.7)	< 0.001

APT, anti-platelet; CKM com., cardiovascular-kidney-metabolic comorbidities; DPP4, dipeptidyl peptidase 4; GLP-1, glucagon-like peptide-1; MRA, mineral receptor antagonist; OAC, oral anticoagulant; ACEi– angiotensin converting enzyme inhibitor; ARB– angiotensin receptor blocker; SGLT2, sodium-glucose co-transporter 2

Table 4 Multivariable logistic regression for treatment

	Non-obese 0 CKM com.	Non-obese 1–2 CKM com.	Non-obese 3 CKM com.	Obese 0 CKM com.	Obese 1–2 CKM com.	Obese 3 CKM com.
	Group 1	Group 2 OR (95% CI)	Group 3 OR (95% CI)	Group 4 OR (95% CI)	Group 5 OR (95% CI)	Group 6 OR (95% CI)
Insulin	Ref.	0.75 (0.39–1.47)	0.66 (0.29–1.48)	0.39 (0.12–1.26)	0.87 (0.45–1.70)	1.96 (0.89–4.35)
Metformin	Ref.	2.84 (1.57–5.19)	1.68 (0.81–3.50)	4.79 (1.48–15.50)	10.05 (5.47–18.47)	1.46 (0.75–2.83)
Sulfonylureas	Ref.	1.34 (0.83–2.16)	1.44 (0.76–2.73)	0.91 (0.28–2.95)	0.94 (0.57–1.55)	0.90 (0.50–1.63)
GLP-1 receptor agonists	Ref.	2.25 (0.47–10.86)	4.82 (0.75–30.76)	4.15 (0.34–50.42)	7.40 (1.57–34.81)	8.16 (1.53–43.52)
SGLT2 inhibitors	Ref.	2.94 (1.20–7.23)	1.31 (0.45–3.84)	1.18 (0.21–6.63)	4.16 (1.71–10.11)	1.06 (0.39–2.88)
DPP4 inhibitors	Ref.	1.14 (0.65–1.98)	1.23 (0.57–2.66)	1.41 (0.43–4.63)	0.90 (0.50–1.62)	1.36 (0.69–2.68)
Insulin with oral glucose-lowering drugs	Ref.	1.66 (1.10–2.49)	1.11 (0.63–1.97)	1.68 (0.66–4.25)	3.13 (2.04–4.78)	1.71 (1.02–2.84)
APT	Ref.	8.61 (3.40-21.85)	18.24 (6.52–51.04)	1.64 (0.28–9.77)	13.36 (5.25–34.02)	12.79 (4.78–34.24)
OAC	Ref.	2.14 (0.28–16.57)	3.25 (0.40-26.61)	10.51 (0.94-117.31)	3.15 (0.41–24.10)	3.45 (0.44–27.29)

APT, anti-platelet; CI, confidence interval; CKM com., cardiovascular-kidney-metabolic comorbidities; DPP4, dipeptidyl peptidase 4; GLP-1, glucagonlike peptide-1; OAC, oral anticoagulant; OR, odds ratio; SGLT2, sodium-glucose co-transporter 2

Adjusted for age, sex, type of diabetes, duration of diabetes, previous CAD, current smoking

Table 5 Event count, incidence rates and multivariable Cox regression for the risk of the primary outcome

	Event count (%)	IR (95% CI)	Unadjusted HR (95% CI)	Adjusted HR* (95% CI)	Adjusted HR† (95% CI)
Group 1– non-obese 0 CKM com.	5 (1.9)	7.21 (2.34–16.83)	Ref.	Ref.	Ref.
Group 2– non-obese 1–2 CKM com.	41 (6.2)	21.37 (15.33–28.98)	2.87 (1.13–7.26)	1.79 (0.69–4.66)	2.55 (0.76–8.56)
Group 3– non-obese 3 CKM com.	19 (14.2)	50.26 (30.26–78.49)	7.09 (2.65-19.00)	3.42 (1.19–9.83)	4.50 (1.20-16.88)
Group 4– obese 0 CKM com.	2 (7.1)	24.48 (2.46–88.42)	3.39 (0.66–17.47)	2.30 (0.44–12.07)	2.34 (0.24–22.86)
Group 5– obese 1–2 CKM com.	57 (7.3)	24.63 (18.65–31.91)	3.36 (1.35–8.38)	1.91 (0.74–4.95)	2.62 (0.78–8.79)
Group 6– obese 3 CKM com.	28 (12)	40.35 (26.81–58.32)	5.64 (2.18–14.62)	2.84 (1.03–7.82)	3.78 (1.06–13.47)

CI, confidence interval; CKM com., cardiovascular-kidney-metabolic comorbidities; HR, hazard ratio; IR, incidence rate per 1000 patient-year

*Adjusted for age and sex

†Adjusted for age, sex, duration of diabetes, current smoking, previous CAD

regression analysis, both non-obese and obese people with 3 CKM comorbidities (Group 3 and Group 6) were associated with a higher risk of experiencing the primary composite outcome (aHR 4.50, 95% CI 1.20-16.88; and aHR 3.78, 95% CI 1.06–13.47, respectively, Table 5).

Interaction analyses

The results of the interaction analyses in metabolically "extremely unhealthy" persons are reported in Fig. 3. The detrimental effect of the presence of 3 CKM comorbidities on the risk of primary composite outcomes was consistent regardless of obesity status (P_{int}=0.824), sex (P_{int}=0.713), and type of DM (P_{int}= 0.702). The association between metabolically "extremely unhealthy" status and risk of the primary outcomes was modified by persons' age (P_{int}= 0.028): the impact of "extremely unhealthy" status appears to be more pronounced in persons aged < 65 years (HR 2.71, 95% CI 1.74–4.22) compared to older individuals (HR 1.37, 95% CI 0.89–2.10).

Discussion

This large prospective cohort study demonstrates: (i) In this contemporary cohort of people with DM, nearly half were non-obese; (ii) Cardiovascular-kidney-metabolic comorbidities were frequent amongst people with DM; (iii) The risk of primary composite outcomes tended to increase progressively with the number of CKM comorbidities, regardless of obesity status, with a higher risk in people with 3 CKM comorbidities; (iv) In "extremely unhealthy" persons, the impact of CKM comorbidities in determining the risk of adverse events was consistent across sex, obesity, and type of DM. However, it appeared more pronounced in persons aged < 65 years compared to older adults.

The demographics of type 2 DM is changing, with an increased number of non-obese persons, compared to the previous decades [8]. In our cohort, approximately half (50.6%) of the people were non-obese. These results are consistent with a recent meta-analysis that reported continuous growth in the incidence of DM amongst normal-weight persons since 1985, with an estimated increase of 36% every 5 years [10]. Similarly, a French national study on hospitalised persons reported a 70% prevalence of non-obese people with DM [27].

Importantly, the prevalence of related comorbidities was high, with less than one-fifth of the cohort presenting with isolated DM. People with a higher burden of comorbidities had a longer duration of DM, possibly related to a progressive effect of the disease on the micro- and macro-vascular system. Non-obese "extremely unhealthy" persons were older, and the prevalence of metabolically "extremely unhealthy" persons was higher in the obese group (22.4% vs. 12.6% in the non-obese "extremely unhealthy"). It is known that there is a large variation in risk at an individual level to developing obesity-associated comorbid diseases and outcomes, which that cannot solely explained by the level of adiposity [28]. Also, the term metabolically healthy obesity (normoglycaemia and absence of dyslipidaemia and hypertension) is a contentious topic with the concept considered to be transient notion in the natural history of obesity. However, compared to lean healthy individuals CV disease is still higher. Our data clearly demonstrate the additional burden to CV risk of CKM comorbidities to either lean or obese persons. It may be that a high burden of comorbidities outweighs obesity and adds a greater risk of worse outcomes, regardless of obesity itself. Moreover, previous studies have shown conflicting results concerning the "obesity paradox", defined as a better outcome for obese people compared with normal or underweight individuals [15, 16, 29–31]. Several explanations have been proposed. BMI may not an accurate measure of adiposity and does not distinguish abdominal and visceral fat from gluteo-femoral fat, with the latter associated with insulin resistance, metabolic disease, and CV complications [32]. Body composition changes with age and older persons tend to have a decrease in muscle and bone mass, with an increased fatty infiltration. Thus, although the overall BMI is lower, this body composition may not necessarily be favourable. This phenomenon, known as sarcopenic obesity, is associated with frailty and increased mortality,

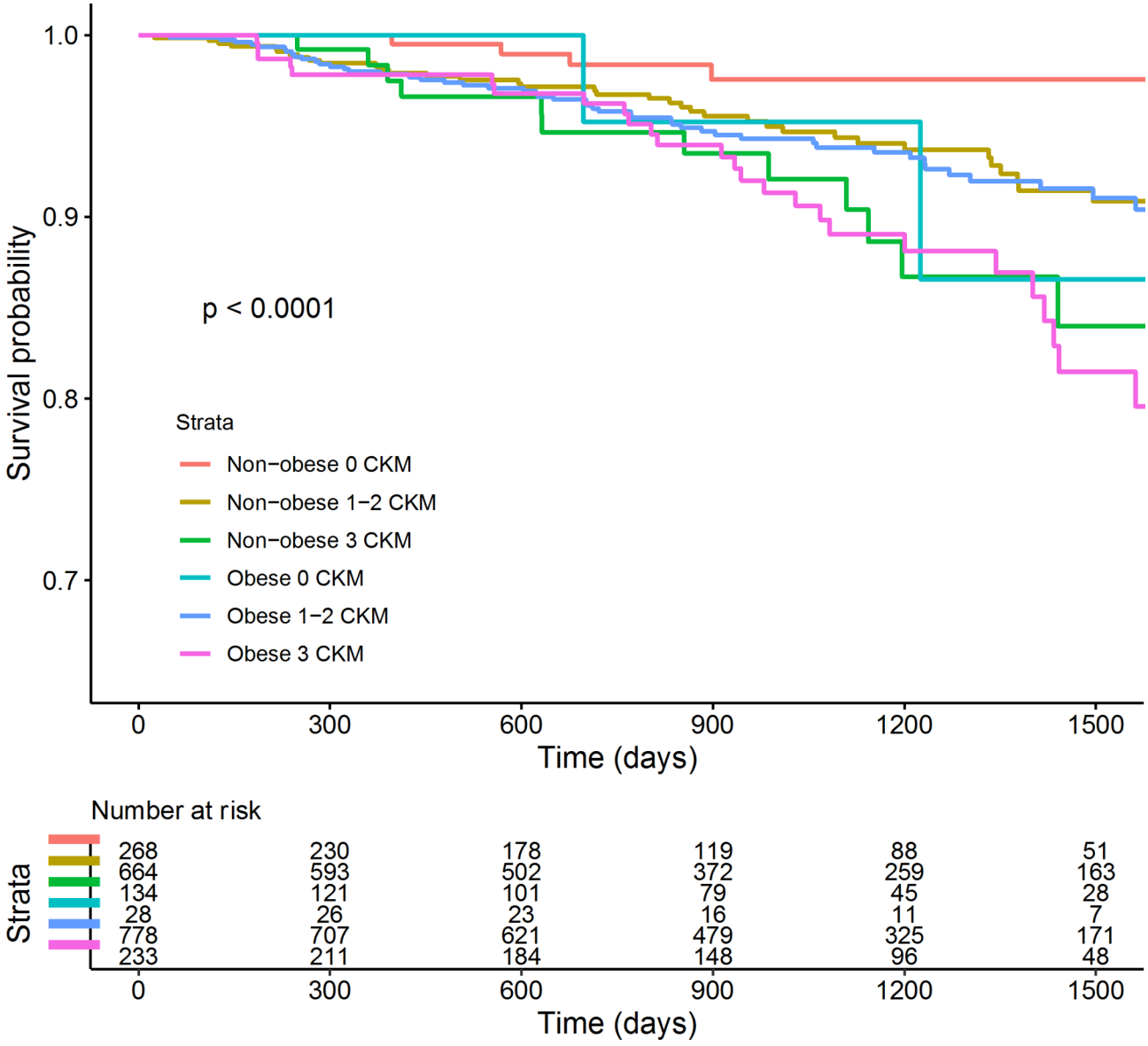

Fig. 2 Kaplan Meier curve for the primary outcome according to the different clinical risk groups. CKM, cardiovascular-kidney-metabolic; Group 1, non-obese with 0 CKM comorbidities; Group 2, non-obese with 1-2 CKM comorbidities; Group 3, non-obese with 3 CKM comorbidities; Group 4, obese with 0 CKM comorbidities; Group 5, obese with 1-2 CKM comorbidities; Group 6, obese with 3 CKM comorbidities

and could at least partially explain the obesity paradox in the elderly [33].

Our results also corroborate previously published data and emphasize the role of multimorbidity, defined as two or more long-term illnesses or diseases, in everyday clinical practice, with an expected increase due to the aging of the population [34]. An US-based outpatient registry with more than 500,000 people with DM found that only 6.4% of the population had no CKM comorbidities, while more than half (51%) had≥3 associated conditions, with the most common ones being hypertension (83%), dyslipidaemia (81%), CAD (32%) and CKD (20%) [35]. Arnold et al. included among CKM comorbidities also CAD, cerebrovascular disease, peripheral artery disease (PAD), atrial fibrillation (AF), HF, and gout, while for the purpose of our analysis, we considered only hypertension, dyslipidaemia, and CKD [35]. Notwithstanding some differences in the definition of CKM comorbidities, these results highlight the high burden of coexisting diseases related to DM.

On this basis, the American Heart Association (AHA) recently published a presidential advisory about cardiovascular-kidney-metabolic (CKM) health [36]. The proposed definition of CKM syndrome is a systemic disorder with pathophysiological interactions among metabolic risk factors (i.e. obesity, DM), CKD, and the

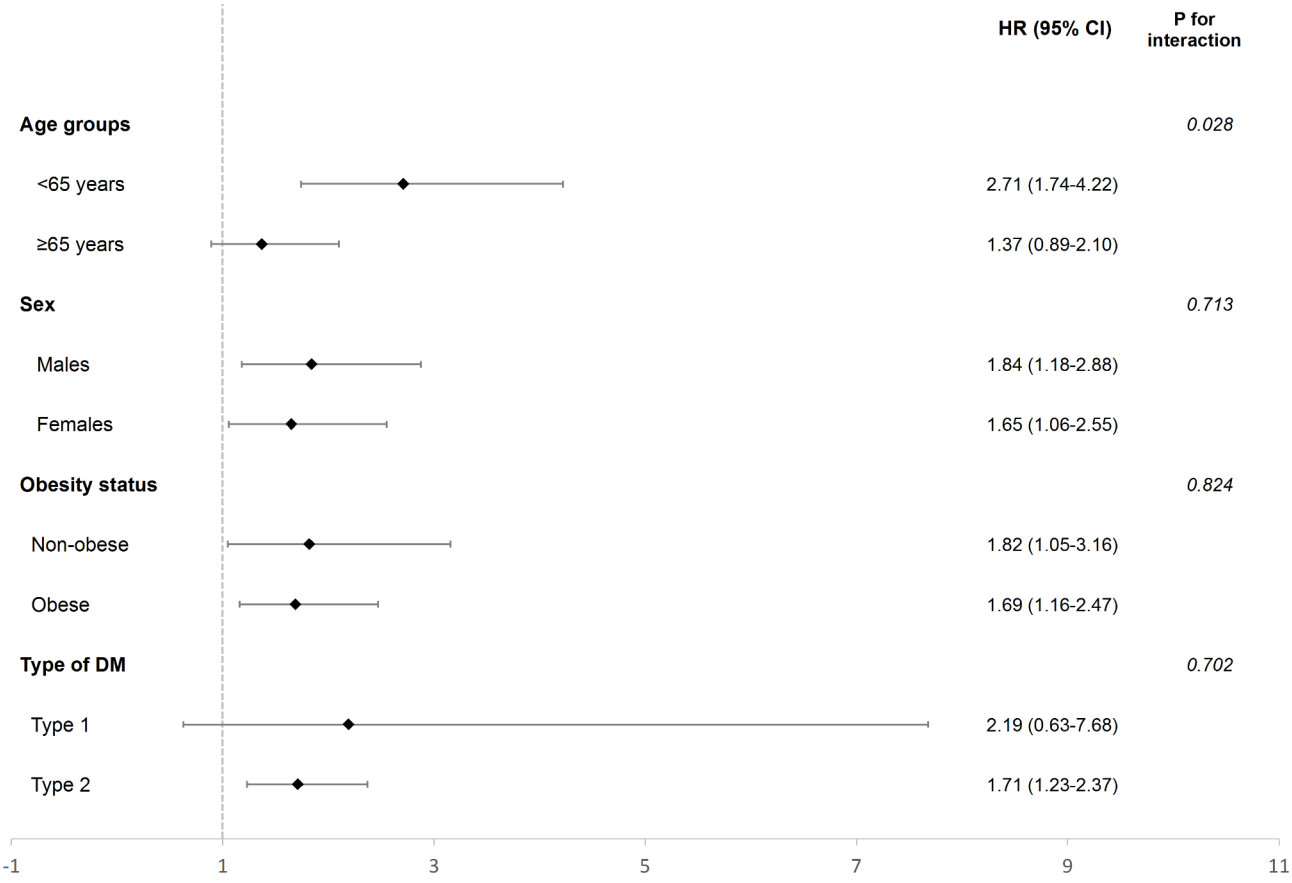

Fig. 3 Interaction analysis on the risk of the primary outcome according to the "extremely unhealthy" status. CI, confidence interval; DM, diabetes mellitus; HR, hazard ratio. Adjusted for age, sex, duration of diabetes, current smoking, previous CAD

cardiovascular system leading to multiorgan dysfunction and a high rate of morbidity and mortality. This syndrome includes both individuals at risk for CV diseases due to the presence of metabolic risk factors or CKD, and individuals with existing CV diseases (i.e. AF, CAD, HF, stroke, PAD) that are potentially related to or are a complication of metabolic risk factors [36].

Importantly, we found progressively higher risk of the primary composite outcome at the increasing number of CKM comorbidities, with poor outcomes associated with the presence of 3 CKM comorbidities, regardless of the obesity status. These results were supported by interaction analysis: in "extremely unhealthy" persons, the impact of CKM comorbidities in determining the risk of adverse events was consistent across the obese and non-obese subgroups. Our data are concordant with a French nationwide cohort study where more than 190,000 people with DM hospitalised for any reason were included. Non-obese and obese "extremely unhealthy" persons were at the highest risk of CV death and major adverse cardiovascular events (MACE) [27]. Similarly, Lassale et al. showed that the risk of CAD was significantly higher in metabolically unhealthy individuals, compared to the metabolically healthy ones, for all the different BMI categories, while among metabolically healthy individuals, overweight and obese ones were at higher risk of CAD than the normal weight counterparts [37].

In our cohort, among "extremely unhealthy" persons, the impact of CKM comorbidities in determining the risk of adverse events was also consistent across sex, and type of DM. People with type 1 DM mainly belonged to the groups less burdened by CKM comorbidities, were younger, and with shorter duration of disease. Probably, we depicted people with type 1 DM in an "early" phase who have a lower risk of adverse events. However, these individuals are at a higher (3–10 fold) risk of MI and CV death compared to the general population [38, 39], and the interaction analysis seems to confirm that the effect of comorbidities is not influenced by the type of DM.

The impact of comorbidities appeared more pronounced in persons aged < 65 years compared to older individuals. A possible explanation is that older persons have an intrinsic high risk of death and CV events, related to the coexistence of numerous physiological and pathological conditions and hence the relative contribution of CKM comorbidities might be reduced. Conversely, in

younger persons, the "extremely unhealthy" status has a more powerful impact on prognosis, since these individuals have a lower baseline risk of adverse events, and the presence of CKM comorbidities considerably increases the overall risk.

Thus, the preference for cardioprotective glucose-lowering agents is crucial to optimise and minimize CV risk in all people with DM, particularly in the youngest ones. To our knowledge, ours is one of the first analysis with granular information about treatment options according to obesity status and the presence of comorbidities. SGLT2 inhibitors or GLP1 RA are frequently initiated in those with high predicted CV risk or selected comorbidities [36]. SGLT2 inhibitors are now well known to have beneficial CV effects both in people with and without DM [40]. Their pleiotropic effects are associated with a protective impact on kidney function decline, HF hospitalizations, and MACE [41–45]. In our cohort, this class of drugs was mainly used in non-obese and obese people with 1–2 CKM comorbidities, thus, further implementation is needed to extend its use to "extremely unhealthy" persons who may benefit [46]. With respect to GLP1 RA, their prescription should be prioritized for those with at least grade II obesity (BMI≥35 kg/m^2), non-optimal glycaemic control, or high insulin dose since their positive impact on weight loss, HF with preserved ejection fraction (HFpEF), reduction in insulin resistance, and in MACEs [47–49]. Consistent with the most recent literature, GLP1 RA, in our cohort, were mainly used in obese people with at least 1 CKM comorbidity, although the number of persons who received these medications was still low (about 6%) and should be further implemented.

Limitations

Our study is observational in design. We did not exclude people with previous CV events and included both type 1 and 2 DM, however this reflects a real-world clinical design. Obesity was defined based on BMI, as it is the most widely used and easily available parameter. However, it does not fully capture body composition (e.g. abdominal distribution of body fat) and sarcopenia might at least partially explain lower body weight, especially in older adults. Furthermore, the number of adverse events in this cohort was low, thus we could not separately analyse the single components of the composite outcome. Finally, despite including multiple covariates in the regression analyses, the presence of residual confounding cannot be excluded. Therefore, these results should be interpreted with caution, as they report associations rather than implying causality.

Conclusion

Both non-obese and obese people with DM with 3 associated cardiovascular-kidney-metabolic comorbidities represent an "extremely unhealthy" phenotype and are at the highest risk of CV adverse events. These results highlight the importance of holistic management and an interdisciplinary approach.

Abbreviations

CV	Cardiovascular risk
CKM	Cardiovascular-kidney-metabolic
MI	Myocardial infarction
HF	Heart failure
DM	Diabetes mellitus
CKD	Chronic kidney disease
BMI	Body mass index
DPP4	Dipeptidyl peptidase 4
GLP1 RA	Glucagon-like peptide-1 receptor agonists
SGLT2	Sodium-glucose co-transporter 2
APT	Antiplatelet
OAC	Oral anticoagulants
SD	Standard Deviation
IQR	Interquartile Range
CAD	Coronary artery disease
OR	Odds Ratio
CI	Confidence Intervals
IR	Incidence Rate
HR	Hazard Ratio
aHR	Adjusted Hazard Ratio
PAD	Peripheral artery disease
AF	Atrial fibrillation
MACE	Major adverse cardiovascular events

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Author contributions

O.J., M.M., G.Y.H.L., and K.N. conceived and designed the analysis; K.N., H.K. J.G. and G.Y.H.L. designed the study; O.J., H.K., K.I., M.H, J.P, A.O., A.W, P.P., WW, and K.N. collected the data. M.M. and S.H.M.L. performed the statistical analysis. O.J., M.M., H.K., S.H.M.L.,, G.Y.H.L and K.N. analysed the data. O.J. and M.M. drafted the original manuscript. K.I. T.B., S.H.M.L., B.H., G.B., M.H., J.P., A.O., A.W., P.P., W.W, edited and revised the manuscript K.N., H.K., U.A, G.Y.H.L and J.G. edited, revised the manuscript, and gave relevant intellectual contribution. All authors read and approved the final manuscript.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

Based on the decision of the Bioethics Committee of the Medical University of Silesia in Katowice, the need for ethical approval was waived (decision no. PCN/0022/KB/126/20).

Consent for publication

All authors gave consent for the publication of the article.

Competing interests

G.Y.H.L. is a consultant and speaker for BMS/Pfizer, Boehringer Ingelheim, Anthos and Daiichi-Sankyo. No fees are received personally. G.Y.H..L is a NIHR Senior Investigator and co-PI of the AFFIRMO project on multimorbidity in AF (grant agreement No 899871), TARGET project on digital twins for personalised management of atrial fibrillation and stroke (grant agreement No 101136244)

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Consent to participate
Not applicable.

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