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ARTICLE

Metabolic health in people living with type 1 diabetes in Belgium: a repeated cross-sectional study

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Abstract

Aims/hypothesis Metabolic abnormalities such as central obesity, insulin resistance, dyslipidaemia and hypertension, often referred to as 'the metabolic syndrome' (or 'combined metabolic abnormalities'), are increasingly being identified in people living with type 1 diabetes, accelerating the risk for CVD. As a result, in recent years, treatment in people living with type 1 diabetes has shifted to improving overall metabolic health rather than glucose control alone. In Belgium, diabetes care for people living with type 1 diabetes is centrally organised. The Initiative for Quality Improvement and Epidemiology in Diabetes, imposed by the Belgian health insurance system, has systematically collected data from patients on intensive insulin therapy treated in all 101 diabetes clinics in Belgium since 2001. The aim of this real-world study is to describe the evolution of treatment and metabolic health, including the prevalence of obesity and combined metabolic abnormalities, in people living with type 1 diabetes over the past 20 years, and to compare the treatment and prevalence of complications between those with and without combined metabolic abnormalities.

Methods We analysed data on adults (≥16 years old) living with type 1 diabetes, who were diagnosed at age ≤45 years and who had a diabetes duration ≥1 year, collected between 2001 and 2022. The evolution of HbA_{1c}, BMI, LDL-cholesterol, systolic BP, lipid-lowering therapy and antihypertensive therapy over time was analysed. The prevalence of individual and multiple metabolic abnormalities according to various definitions of the metabolic syndrome/combined metabolic abnormalities was analysed, and the association between combined metabolic abnormalities and metabolic health indicators, complications and treatment was investigated in the 2022 data.

Results The final dataset consisted of 26,791 registrations of adults living with type 1 diabetes collected between 2001 and 2022. Although glycaemic and lipid control generally improved over time, the prevalence of obesity strongly increased (12.1% in 2001 vs 21.7% in 2022, $p<0.0001$), as did the presence of combined metabolic abnormalities (WHO criteria: 26.9% in 2001 vs 42.9% in 2022 in women, $p<0.0001$; 30.4% in 2001 vs 52.1% in 2022 in men, $p<0.0001$; WHO criteria without albuminuria: 22.3% in 2001 vs 40.6% in 2022 in women, $p<0.0001$; 25.1% in 2001 vs 49.2% in 2022 in men, $p<0.0001$; NCEP-ATPIII criteria: 39.9% in 2005 vs 57.2% in 2022 in women, $p<0.0001$; 40.8% in 2005 vs 60.9% in 2022 in men, $p<0.0001$; IDF criteria: 43.9% in 2005 vs 59.3% in 2022 in women, $p<0.001$; 33.7% in 2005 vs 50.0% in 2022 in men, $p<0.0001$). People with combined metabolic abnormalities had higher glucose levels compared to those without combined metabolic abnormalities (HbA_{1c} >58 mmol in men: 48.9% vs 36.9%; HbA_{1c} >58 mmol in women: 53.3% vs 41.1%, $p<0.0001$). People with combined metabolic abnormalities were more often treated with adjunct therapies such as metformin, sodium–glucose transport protein 2 inhibitors and glucagon-like peptide-1 receptor agonists. In both men and women, the presence of combined metabolic abnormalities was strongly related to the presence of eye complications, peripheral neuropathy, chronic kidney disease and CVD, corrected for age, diabetes duration and HbA_{1c}.

Conclusions/interpretation Overweight, obesity and combined metabolic abnormalities are increasingly being identified in people living with type 1 diabetes, further accelerating the risk of microvascular and macrovascular complications. Early identification of the presence of combined metabolic abnormalities should enable therapeutic interventions to be modified towards multifactorial approaches, with attention to education on avoidance of overweight (e.g. dietary counselling) in addition to strict glycaemic control and intensification of use of antihypertensive agents and statins. Use of adjunct therapies in this population as a tool should be explored more thoroughly to reduce risk of complications.

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Research in context

What is already known about this subject?

- In recent decades, obesity has increased due to more sedentary lifestyles and unhealthy diets
- Although people living with type 1 diabetes are stereotypically thought of as being lean, obesity is a growing emergency in this population

What is the key question?

- How has metabolic health (including obesity and combined metabolic abnormalities) evolved in people living with type 1 diabetes over the last 20 years, and what is the relationship between combined metabolic abnormalities and treatment/complications in this population?

What are the new findings?

- In this large real-world observational study of data collected since 2001 for adults living with type 1 diabetes, we observed an increase in the prevalence of obesity and combined metabolic abnormalities in people with type 1 diabetes
- The presence of combined metabolic abnormalities in people living with type 1 diabetes was positively associated with the presence of diabetes complications, corrected for age, diabetes duration and HbA_{1c}

How might this impact on clinical practice in the foreseeable future?

- Early identification of the presence of combined metabolic abnormalities, together with a multifactorial approach to type 1 diabetes management, including attention to education on avoidance of overweight (e.g. dietary counselling), are needed, and the use of adjunct therapies in this population should be explored more thoroughly as a tool to reduce the risk of complications

Keywords Combined metabolic abnormalities · Diabetes complications · Diabetes treatment · Metabolic health · Metabolic syndrome · Obesity · Real-world data · Type 1 diabetes

Abbreviations

CSII	Continuous subcutaneous insulin infusion
$eGDR_{WC}$	Estimated glucose disposal rate based on waist circumference
$eGDR_{BMI}$	Estimated glucose disposal rate based on BMI
GEE	Generalised estimating equations
GLP1	Glucagon-like peptide-1
IQED	Initiative for Quality Improvement and Epidemiology in Diabetes
NCEP-ATPIII	National Cholesterol Education Program Adult Treatment Panel III
SGLT2	Sodium–glucose cotransporter 2
TG	Triglycerides
WC	Waist circumference

Introduction

Since the DCCT/Epidemiology of Diabetes Interventions and Complications trial demonstrated a reduction in chronic complications of diabetes in people on intensive insulin therapy [1–3], treatment in type 1 diabetes has mainly focused on reducing blood glucose levels. However, the profile of people living with type 1 diabetes is evolving, with overweight and obesity coming to the fore, and overall metabolic health, rather than glucose control alone, contributing to outcomes [4, 5]. People living with type 1 diabetes still have an almost threefold higher mortality rate compared with the general population, with CVD being a major cause of this increased mortality risk [6, 7]. In addition, achieving and maintaining strict glucose control, which is the primary therapeutic goal in most patients living with type 1 diabetes, requires a high level of self-management and follow-up, but also increases the risk for insulin-induced weight gain, and may thus aggravate cardiovascular risk [8].

The presence of a combination of metabolic abnormalities, including central obesity, insulin resistance, dyslipidaemia and hypertension, in addition to hyperglycaemia, often referred to by clinicians as 'the metabolic syndrome' or 'combined metabolic abnormalities', is a hallmark of type 2 diabetes and increases the risk of CVD in this population as well as in the general population [9, 10]. This combination of metabolic abnormalities is also increasingly found in people living with type 1 diabetes, partly related to lifestyle choices and rising obesity rates in the general population, but also secondary to insulin therapy, as insulin-induced weight gain may induce peripheral insulin resistance [11]. This cluster of metabolic abnormalities may be a target for intervention, identifying people living with type 1 diabetes at high risk of developing CVD who may benefit from adjunct treatments that address insulin resistance and cardiometabolic risk [10, 12].

The aim of this real-world observational study is to describe the evolution of treatment and metabolic health, including the prevalence of obesity and combined metabolic abnormalities, over the past 20 years in people in Belgium living with type 1 diabetes, and to compare the treatment and prevalence of complications between those with and without combined metabolic abnormalities in the setting of centrally organised diabetes care with free-of-charge access to diabetes education, regular follow-up by a multidisciplinary team, and reimbursement of medication, sensors and pumps to manage diabetes.

Methods

Study population We used data from the Initiative for Quality Improvement and Epidemiology in Diabetes (IQED), a national project allowing monitoring and improvement of the quality of care for people living with diabetes in Belgium, and study of their epidemiology [13, 14].

For this study, data on adults (aged ≥18 years until 2015; aged ≥16 years from 2016) living with type 1 diabetes were cross-sectionally collected between 2001 and 2022. Patients with a history of pancreas or islet cell transplantation, dementia or pregnant women were excluded from the IQED study. Data from people treated with continuous subcutaneous insulin infusion (CSII) were not collected between 2006 and 2014. Each centre was asked to review their medical records and complete a standardised electronic questionnaire using the patient's most recent data from the previous year (the audit period) for 10% of the total number of people living with diabetes and treated at their centre. The 10% sample was defined by the first letter of the family name, chosen randomly at the start of each data collection period. Data were pseudonymised. More information about the data collected and the data collection process is available online [13].

Final dataset The people living with type 1 diabetes were defined based on the clinical diagnosis encoded in the electronic patient file. The IQED database contained 40,449 registrations of adults living with type 1 diabetes. We excluded registrations for people for whom information was missing: sex (n=1), age (n=1), diabetes duration (n=627), HbA_{1c} (n=752), LDL-cholesterol (n=3761), HDL-cholesterol (n=3275), triglycerides (TG) (n=3018), lipid-lowering therapy (n=1277), antihypertensive therapy (n=1183), systolic BP (n=927), diastolic BP (n=951) or BMI (n= 3220). To eliminate mis-classified type 2 diabetes as much as possible, people with an age at diagnosis ≥45 years (n=4596) and a diabetes duration of less than 1 year (n=617) were also excluded. Thus the final dataset consisted of 26,791 registrations of adults living with type 1 diabetes cross-sectionally collected between 2001 and 2022.

Parameters We used various definitions of the metabolic syndrome/combined metabolic abnormalities: (1) the WHO definition [10]; (2) the National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATPIII) definition [15], which is equivalent to the Joint Interim Statement of the International Diabetes Federation Task Force on Epidemiology and Prevention, National Heart, Lung and Blood Institute, American Heart Association, World Heart Federation, International Atherosclerosis Society and the International Association for the Study of Obesity [16] using their waist circumference (WC) thresholds; and (3) the International Diabetes Federation (IDF) definition [17]. In addition to diabetes, the WHO definition of the metabolic syndrome/combined metabolic abnormalities requires the presence of two or more of the following conditions: obesity (BMI >30 kg/m^2), hypertension (BP ≥140/90 mmHg and/or treatment with antihypertensive drugs), triglycerides ≥1.7 mmol/l (≥150 mg/dl), HDL-cholesterol <0.9 mmol/l (<35 mg/dl) in men or <1 mmol/l (<40 mg/dl) in women and/or treatment with lipid-lowering drugs, or albuminuria (albumin 0.3 g/l [>30 mg/dl]). Applying the NCEP-ATPIII definition in people living with diabetes, the metabolic syndrome/combined metabolic abnormalities requires the presence of two or more of the following conditions: WC ≥102 cm in men (≥88 cm in women), hypertension (BP ≥130/85 mmHg and/or treatment with antihypertensive drugs), TG ≥1.7 mmol/l (≥150 mg/dl), or HDL-cholesterol <1 mmol/l (<40 mg/dl) in men/<1.3 mmol/l (<50 mg/dl) in women and/or treatment with lipid-lowering drugs. In addition to the presence of central obesity (WC >94 cm in men, >80 cm in women), the IDF definition of the metabolic syndrome/combined metabolic abnormalities in people living with diabetes, requires the presence of one or more of the following conditions: hypertension (BP ≥130/85 mmHg and/or treatment with antihypertensive drugs), TG ≥1.7 mmol/l (≥150 mg/dl), or HDL-cholesterol <1 mmol/l (<40 mg/dl) in men/<1.3

mmol/l (<50 mg/dl) in women and/or treatment with lipid-lowering drugs.

The estimated glucose disposal rate (eGDR) was used as a measure of insulin resistance, and was calculated using the formula: $eGDR_{WC} = 21.158 + (-0.09 \times WC, \text{ in cm}) + (-3.407 \times \text{presence or absence of hypertension, where presence} = 1/\text{absence} = 0) + (-0.551 \times HbA_{1c}, \%)$, whereby the presence of hypertension was defined as BP ≥140/90 mmHg or current use of any antihypertensive drugs [18]. As WC was only reported from audit 4 onwards and for the minority of the patients, the following formula was used as an alternative: $eGDR_{BMI} = 19.02 - (0.22 \times \text{BMI, in kg/m}^2) - (3.26 \times \text{hypertension, presence} = 1/\text{absence} = 0) - (0.61 \times HbA_{1c}, \%)$ [11].

LDL-cholesterol was calculated by the Friedewald formula for patients with TG <4.52 mmol/l (<400 mg/dl), regardless of whether the blood sample was obtained under fasting or non-fasting conditions [19, 20].

Statistical analysis Results are expressed as proportions for categorical variables, mean ± SD for normally distributed variables, or median (IQR) for non-normally distributed variables.

The statistical significance of the trend over time for study population characteristics and the individual metabolic abnormalities was tested using generalised estimating equations (GEE), using logistic regression for dichotomous outcome variables and the normal probability distribution for continuous outcome variables, with exchangeable correlation structure (diabetes centre and patient) and audit year (defined as the midpoint of the audit year) as continuous explanatory variables.

Statistical comparisons of mean HbA_{1c}, BMI, LDL-cholesterol, systolic BP or the proportion of people using lipid-lowering and antihypertensive drugs between 2001 and 2022 were tested using GEE as described above, with audit year as the categorical explanatory variable. Comparisons were adjusted using the Tukey method.

Pairwise differences in the prevalence of combined metabolic abnormalities by sex between 2001 and 2022 were analysed using GEE as described above, with audit year as the categorical explanatory variable and comparisons adjusted using the Tukey method. Statistical analyses were also adjusted for age (continuous) and diabetes duration (continuous) using GEE. The GEE model predictions are presented with the corresponding 95% CI.

Statistical comparisons of metabolic health indicators and treatment rates between people with and without combined metabolic abnormalities in 2022 was tested using GEE as described above, with the presence of combined metabolic abnormalities as the categorical explanatory variable and comparisons adjusted using the Tukey method. Analysis of the prevalence of complications by sex was adjusted for age (continuous) and diabetes duration (continuous). The GEE model predictions are presented with the corresponding 95% CI. Analyses were repeated with additional adjustment for HbA_{1c} (continuous) or smoking status (categorical).

All p values were two-sided. p values <0.05 were considered statistically significant. Data analyses were performed using SAS software version 9.4 (SAS Institute, USA).

Results

Population characteristics Table 1 shows the general characteristics of the study population for each audit. The number of people included in each audit increased over time. Since 2001, the general characteristics of the study population have significantly changed: people living with type 1 diabetes are older, have a longer diabetes duration and a younger age at diagnosis. The proportion of smokers significantly decreased, whereas BMI and WC significantly increased. Insulin resistance, as measured by a decrease in $eGDR_{WC}$ and $eGDR_{BMI}$, significantly increased. The proportion of CSII users also increased tenfold from 2% in 2001 to 20% in 2022.

Evolution of HbA_{1c}, BMI, lipids and BP The mean BMI increased from 25.4 ± 4.2 kg/m^2 in 2001 to 26.7 ± 4.8 kg/m^2 in 2022 (p<0.0001), whereas the mean HbA_{1c} decreased from 64 ± 18 mmol/mol (8.0 ± 1.6%) in 2001 to 59 ± 13 mmol/mol (7.6 ± 1.2%) in 2022 (p<0.0001) (Fig. 1a). The mean LDL-cholesterol value decreased from 2.9 ± 0.9 mmol/l in 2001 to 2.3 ± 0.8 mmol/l in 2022 (p<0.0001), which is mainly explained by an increase in the rate of lipid-lowering therapy from 12.7% in 2001 to 39.5% in 2011 (p<0.0001) and 48.1% in 2022 (p<0.0001 vs 2011) (Fig. 1b). The mean systolic BP value did not change over time (129 ± 18 mmHg in 2001 vs 129 ± 17 mmHg in 2022). The rate of antihypertensive therapy increased from 24.3% in 2001 to 36.3% in 2007 (p<0.0001) and remained stable afterwards (Fig. 1c).

Evolution of metabolic abnormalities in people living with type 1 diabetes Table 2 shows the evolution of the presence of the individual metabolic abnormalities used by the various definitions of the metabolic syndrome/combined metabolic abnormalities. The proportion of people with below-target HDL-cholesterol or receiving lipid-lowering therapy strongly increased, but the prevalence of hypertriglyceridaemia remained stable. The prevalence of hypertension slightly increased. The prevalence of obesity doubled, and the proportion of people with above-target WC increased. The prevalence of albuminuria did not change significantly from 2001.

Table 1 General characteristics of people living with type 1 diabetes

Audit	Audit number												Trend since 2001, *p* value	Trend since 2016, *p* value
	1	2	3	4	5	6	7	8	9	10	11	12		
Audit period	11/2000–11/2001	10/2001–09/2002	03/2003–02/2004	02/2005–01/2006	10/2006–09/2007	03/2008–03/2009	09/2010–08/2011	12/2013–12/2014	10/2015–09/2016	10/2017–09/2018	03/2020–02/2021	10/2021–09/2022		
Audit year (midpoint)	2001	2002	2003	2005	2007	2008	2011	2014	2016	2018	2020	2022		
Number of patients	1256	1399	1459	1652	2412	2373	2502	2570	2650	2714	2815	2989		
Men	718 (57.2)	799 (57.1)	840 (57.6)	934 (56.5)	1384 (57.4)	1423 (60.0)	1507 (60.2)	1509 (58.7)	1527 (57.6)	1578 (58.1)	1612 (57.3)	1697 (56.8)	ns	ns
Age, years	42.3 (33.3–52.3)	42.2 (33.2–52.2)	41.7 (32.7–52.7)	43.6 (33.6–52.6)	43.2 (34.2–53.2)	44.7 (34.7–53.7)	45.2 (34.2–55.2)	45.5 (35.5–57.5)	46.2 (34.2–57.2)	46.2 (34.2–57.2)	46.7 (34.7–58.7)	46.2 (35.2–58.2)	<0.0001	<0.0001
Diabetes duration, years	17.3 (9.3–27.3)	17.2 (9.2–27.2)	17.7 (9.7–28.7)	17.7 (9.6–29.6)	18.2 (10.2–29.2)	17.7 (9.7–28.7)	19.2 (10.2–31.2)	20.5 (11.5–32.5)	21.0 (11.6–32.2)	21.2 (11.8–32.2)	21.7 (12.7–33.7)	22.2 (12.8–33.3)	<0.0001	<0.0001
Age at diagnosis, years	24.0 (15.0–33.0)	24.0 (15.0–33.0)	23.0 (14.0–32.0)	24.0 (14.0–32.0)	24.0 (14.0–32.0)	24.0 (15.0–33.0)	24.0 (15.0–32.0)	24.0 (14.0–33.0)	23.0 (14.0–32.1)	23.0 (13.6–32.0)	23.0 (13.0–31.5)	22.9 (13.0–31.5)	<0.0001	ns
Smoker	304 (25.7) (*N*=1185)	337 (24.7) (*N*=1365)	320 (22.6) (*N*=1418)	349 (22.6) (*N*=1543)	542 (23.4) (*N*=2315)	526 (23.3) (*N*=2257)	546 (23.0) (*N*=2374)	495 (20.7) (*N*=2397)	513 (20.5) (*N*=2501)	552 (21.4) (*N*=2580)	520 (19.3) (*N*=2690)	548 (19.2) (*N*=2848)	<0.0001	ns
BMI, kg/m^2	25.4 ± 4.2	25.2 ± 4.0	25.4 ± 4.3	25.6 ± 4.2	25.5 ± 4.3	25.8 ± 4.4	26.0 ± 4.7	26.0 ± 4.5	26.1 ± 4.6	26.2 ± 4.7	26.8 ± 4.8	26.7 ± 4.8	<0.0001	<0.0001
WC, cm				90.6 ± 16.3 (*N*= 317)	89.5 ± 13.4 (*N*= 985)	90.7 ± 13.4 (*N*=1066)	91.9 ± 13.4 (*N*=1107)	91.0 ± 13.1 (*N*=1086)	92.0 ± 14.3 (*N*=1153)	91.5 ± 14.0 (*N*=1081)	94.1 ± 14.4 (*N*= 899)	94.0 ± 14.9 (*N*=1028)	<0.0001	<0.0001
$eGDR_{WC}$, mg/kg/min				6.9 ± 2.6 (*N*= 317)	7.1 ± 2.4 (*N*= 985)	6.9 ± 2.5 (*N*=1066)	6.8 ± 2.4 (*N*=1107)	7.0 ± 2.4 (*N*=1086)	6.8 ± 2.5 (*N*=1153)	6.9 ± 2.5 (*N*=1081)	6.4 ± 2.5 (*N*= 899)	6.6 ± 2.6 (*N*=1028)	<0.0001	<0.01
$eGDR_{BMI}$, mg/kg/min	7.2 ± 2.3	7.3 ± 2.3	7.1 ± 2.3	6.9 ± 2.2	7.0 ± 2.2	6.9 ± 2.3	6.9 ± 2.3	6.9 ± 2.2	6.9 ± 2.2	6.9 ± 2.3	6.6 ± 2.3	6.9 ± 2.3	<0.0001	≤0.05
CSII	23 (1.8) (*N*=1246)	53 (3.8) (*N*=1389)	18 (1.2) (*N*=1446)	/	/	/	/	/	280 (10.7) (*N*=2615)	344 (12.9) (*N*=2658)	416 (15.0) (*N*=2765)	577 (19.7) (*N*=2933)	<0.0001	<0.0001

Values are *n* (%) for categorical variables and median (IQR) or mean ± SD for continuous variables

Change over time of the general characteristics of people living with type 1 diabetes was analysed from 2001 until 2022 (trend since 2001) and from 2016 until 2022 (trend since 2016). CSII users were not eligible for inclusion in the IQED study between audit 4 and audit 9. Data on smoking habits, WC and CSII use were only available for the indicated populations (*N*). For WC, the trend since 2001 is actually measured from 2005, as WC data are only available from audit 4 onwards

N, population size; *n*, number of observations; ns, not significant

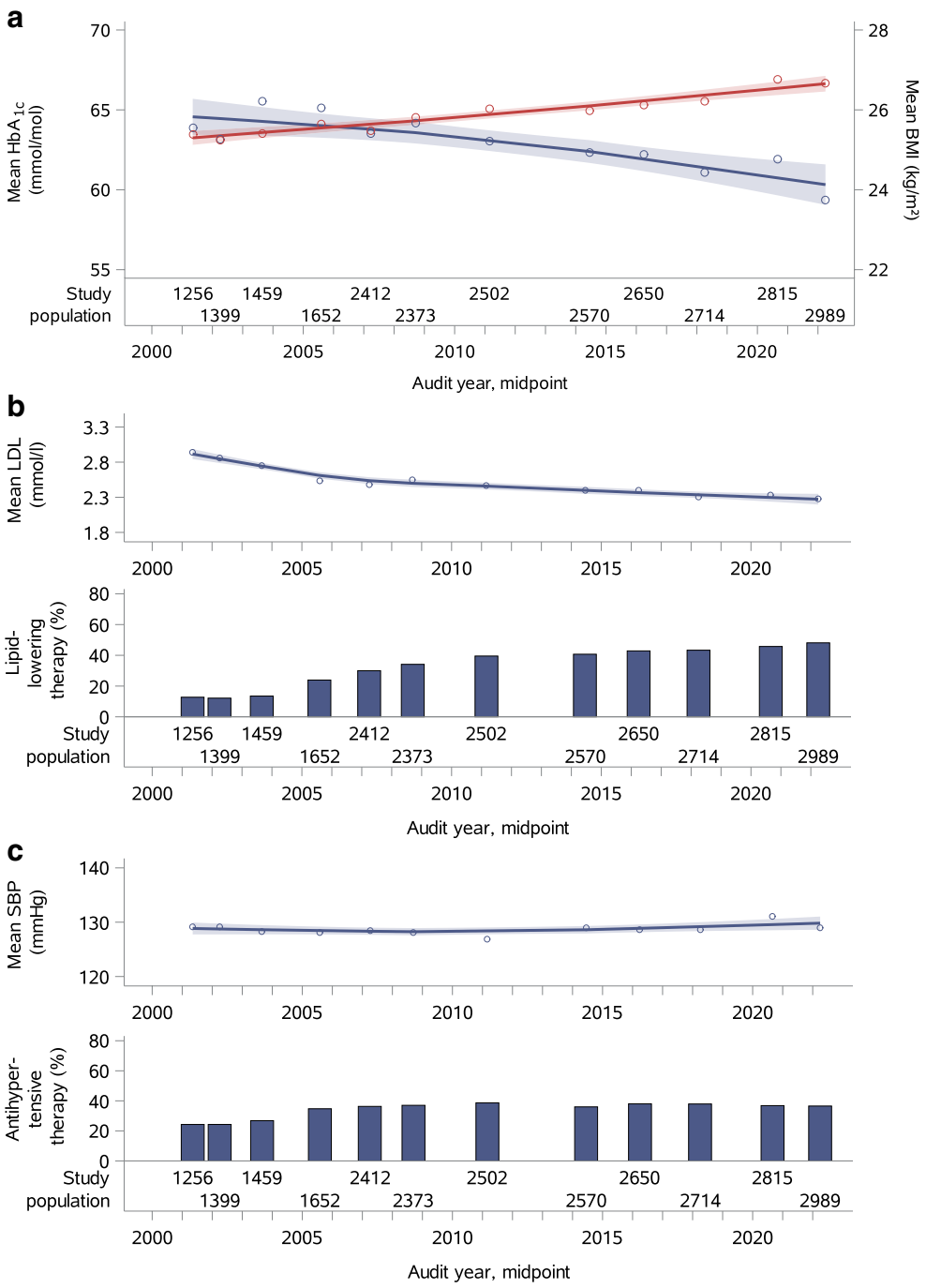

Fig. 1 (**a**) Evolution of the mean HbA_{1c} value (blue circles) and mean BMI value (red circles) over the audit years. (**b**) Evolution of the mean LDL-cholesterol value (blue circles) and the proportion of people living with type 1 diabetes and treated with lipid-lowering therapy (blue bars) over the audit years. Lipid-lowering therapy was defined as use of statins, fibrates (included in the data collection from 2006) or ezetimibe (included in the data collection from 2011). (**c**) Evolution of the mean systolic BP value (blue circles) and the proportion of people living with type 1 diabetes and treated with antihypertensive therapy (blue bars) over the audit years. Antihypertensive therapy was defined as use of ACE inhibitors (including sartans) or other antihypertensive drugs (included in the data collection from 2006). The solid lines are the fitted LOESS curves; the shaded bands represent the 95% CI of the fitted LOESS curve. The size of the study population in each audit year is indicated below the graphs. SBP, systolic BP

Between 2001 and 2022, the prevalence of combined metabolic abnormalities based on the various definitions of the metabolic syndrome/combined metabolic abnormalities increased (Fig. 2). Based on the WHO criteria, the prevalence of combined metabolic abnormalities increased from 26.9% in 2001 to 42.9% in 2022 in women ($p<0.0001$), and from 30.4% in 2001 to 52.1% in 2022 in men ($p<0.0001$). This increase remained when albuminuria was removed from the definition (from 22.3% to 40.6% in women [$p<0.0001$] and from 25.1% to 49.2% in men [$p<0.0001$]). Based on the NCEP-ATPIII criteria, the prevalence of combined metabolic abnormalities increased from 39.9% in 2005 to 57.2% in 2022 in women ($p<0.0001$) and from 40.8% in 2005 to 60.9% in 2022 in men ($p<0.0001$). Use of the IDF criteria (which require the presence of central obesity) showed an increase in the prevalence of combined metabolic abnormalities from 43.9% in 2005 to 59.3% in 2022 in women ($p<0.001$) and from 33.7% in 2005 to 50.0% in 2022 in men ($p<0.0001$).

Table 2 Evolution of metabolic abnormalities in people living with type 1 diabetes

Audit	Audit number													
	1	2	3	4	5	6	7	8	9	10	11	12		
Audit period	11/2000–11/2001	10/2001–09/2002	03/2003–02/2004	02/2005–01/2006	10/2006–09/2007	03/2008–03/2009	09/2010–08/2011	12/2013–12/2014	10/2015–09/2016	10/2017–09/2018	03/2020–02/2021	10/2021–09/2022	Trend since 2001, *p* value	Trend since 2016, *p* value
Audit year, midpoint	2001	2002	2003	2005	2007	2008	2011	2014	2016	2018	2020	2022		
Number of patients	1256	1399	1459	1652	2412	2373	2502	2570	2650	2714	2815	2989		
Reduced HDL-cholesterol[a]														
<0.9 mmol/l in men (<1 mmol/l in women)	207 (16.5)	209 (14.9)	224 (15.4)	433 (26.2)	770 (31.9)	872 (36.7)	1043 (41.7)	1097 (42.7)	1178 (44.5)	1219 (44.9)	1333 (47.4)	1502 (50.3)	<0.0001	<0.0001
<1 mmol/l in men (<1.3 mmol/l in women)	292 (23.2)	281 (20.1)	293 (20.1)	504 (30.5)	863 (35.8)	984 (41.5)	1146 (45.8)	1193 (46.4)	1263 (47.7)	1311 (48.3)	1449 (51.5)	1634 (54.7)	<0.0001	<0.0001
TG ≥1.7 mmol/l	217 (17.3)	213 (15.2)	253 (17.3)	237 (14.3)	346 (14.3)	358 (15.1)	362 (14.5)	362 (14.1)	369 (13.9)	404 (14.9)	433 (15.4)	453 (15.2)	ns	ns
Hypertension[b]														
BP ≥140/90 mmHg	539 (42.9)	590 (42.2)	623 (42.7)	753 (45.6)	1172 (48.6)	1151 (48.5)	1230 (49.2)	1256 (48.9)	1325 (50.0)	1357 (50.0)	1512 (53.7)	1499 (50.2)	<0.0001	<0.01
BP ≥130/85 mmHg	760 (60.5)	827 (59.1)	871 (59.7)	992 (60.0)	1536 (63.7)	1482 (62.5)	1513 (60.5)	1640 (63.8)	1692 (63.8)	1721 (63.4)	1949 (69.2)	1927 (64.5)	<0.0001	ns
BMI >30 kg/m^2	152 (12.1)	159 (11.4)	178 (12.2)	240 (14.5)	319 (13.2)	374 (15.8)	436 (17.4)	449 (17.5)	456 (17.2)	501 (18.5)	643 (22.8)	648 (21.7)	<0.0001	<0.0001
Central obesity														
WC >102 cm in men (>88 cm in women)				94 (29.7) (*N*=317)	232 (23.6) (*N*=985)	311 (29.2) (*N*=1066)	352 (31.8) (*N*=1107)	320 (29.5) (*N*=1086)	397 (34.4) (*N*=1153)	349 (32.3) (*N*=1081)	328 (36.5) (*N*=899)	394 (38.3) (*N*=1028)	<0.0001	ns
WC >94 cm in men (>80 cm in women)				154 (48.6) (*N*=317)	452 (45.9) (*N*=985)	517 (48.5) (*N*=1066)	581 (52.5) (*N*=1107)	561 (51.7) (*N*=1086)	618 (53.6) (*N*=1153)	571 (52.8) (*N*=1081)	545 (60.6) (*N*=899)	620 (60.3) (*N*=1028)	<0.0001	<0.0001
Albuminuria	184 (17.4) (*N*=1060)	170 (14.6) (*N*=1166)	187 (15.2) (*N*=1232)	249 (17.3) (*N*=1436)	321 (15.7) (*N*=2042)	337 (16.4) (*N*=2057)	306 (14.3) (*N*=2145)	300 (13.9) (*N*=2163)	314 (14.5) (*N*=2170)	323 (14.8) (*N*=2180)	312 (14.2) (*N*=2190)	319 (13.5) (*N*=2367)	ns	ns

Values are *n* (%) for categorical variables

Data on WC and albuminuria were only available for the indicated populations (*N*). For WC, the trend since 2001 is actually measured from 2005, as WC data are only available from audit 4 onwards

[a]The presence of reduced HDL-cholesterol is defined by the thresholds given in the rows below and/or use of lipid-lowering therapy

[b]The presence of hypertension is defined by the thresholds given in the rows below and/or use of antihypertensive therapy

N, population size; *n*, number of observations; ns, not significant

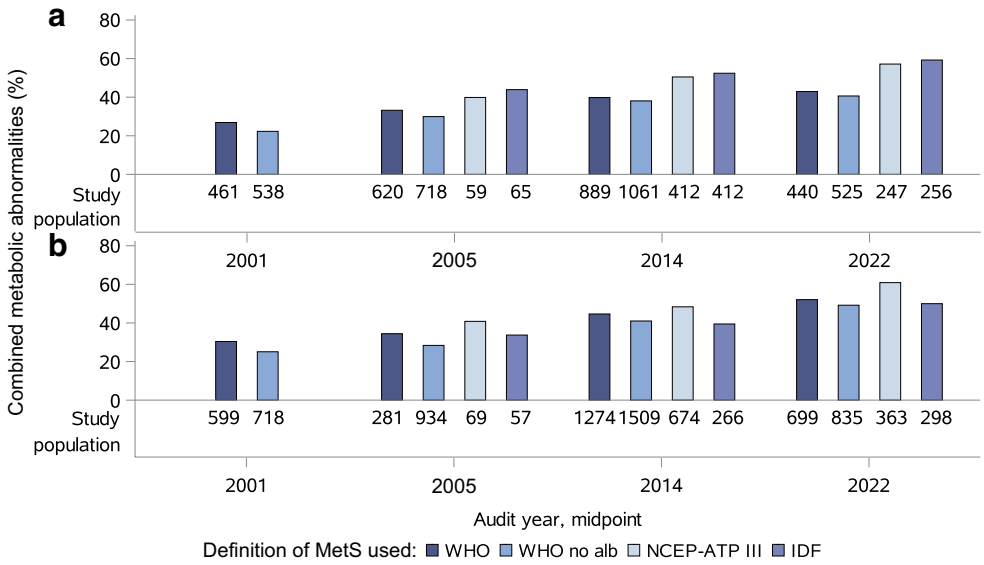

Fig. 2 Prevalence of combined metabolic abnormalities in 2001, 2005, 2014 and 2022 for women (**a**) and men (**b**), according to the various definitions of the metabolic syndrome/combined metabolic abnormalities. The sizes of the study populations are indicated below the bars. MetS, combined metabolic abnormalities (metabolic syndrome); no alb, no albuminuria

Similar increases were seen between 2005 and 2022 after adjustment for age and diabetes duration: from 27.5% (95% CI 23.2, 32.3) to 40.2% (37.2, 43.3) in women ($p<0.01$) and from 31.7% (27.7, 36.1) to 49.7% (46.9, 52.5) in men ($p<0.0001$) using the WHO criteria; from 21.8% (18.2, 25.8) to 38.2% (35.5, 40.9) in women ($p<0.0001$) and from 24.7% (21.4, 28.4) to 46.4% (43.9, 48.9) in men ($p<0.0001$) using the WHO criteria without albuminuria; from 43.3% (35.6, 51.4) to 56.9% (51.8, 61.9) in women (not significant) and from 42.3% (35.1, 49.9) to 58.7% (54.5,62.8) in men ($p<0.01$) using the NCEP-ATPIII criteria; and from 42.5% (36.0,49.3) to 60.6% (56.2,64.9) in women ($p<0.001$) and from 28.2% (22.1, 35.1) to 52.7% (49.1, 56.2) in men ($p<0.0001$) using the IDF criteria.

Metabolic health indicators, diabetes complications and treatment in people with and without combined metabolic abnormalities People living with type 1 diabetes with combined metabolic abnormalities (defined using the WHO criteria without albuminuria) were less often treated with CSII, but use of metformin was threefold higher in those with combined metabolic abnormalities compared to those without combined metabolic abnormalities. In addition to antihypertensive and lipid-lowering drugs, those with combined metabolic abnormalities received sodium–glucose cotransporter 2 (SGLT2) inhibitors and glucagon-like peptide-1 (GLP1) receptor agonists more frequently (Table 3).

Except for smoking, both men and women with combined metabolic abnormalities had worse metabolic health compared with people living with type 1 diabetes without combined metabolic abnormalities (Table 3). As expected, people with combined metabolic abnormalities had a higher prevalence of all individual metabolic abnormalities included in the cluster, but also had a significantly higher prevalence of elevated HbA_{1c} (>58 mmol/mol or >7.5%) and lower $eGDR_{WC}$ and $eGDR_{BMI}$.

Furthermore, the presence of combined metabolic abnormalities was associated with a higher prevalence of micro- and macrovascular complications, corrected for age and diabetes duration (Table 3). The prevalence of eye complications was about 50% higher in both men and women with combined metabolic abnormalities compared to those without combined metabolic abnormalities. The prevalence of peripheral neuropathy was twice as high in both men and women with combined metabolic abnormalities compared to those without combined metabolic abnormalities. Chronic kidney disease and CVD were 65% and 80%, respectively, more prevalent in men with combined metabolic abnormalities compared to those without combined metabolic abnormalities, and twice as prevalent in women with combined metabolic abnormalities compared to those without combined metabolic abnormalities. The results did not change upon additional adjustment for HbA_{1c} or smoking (data not shown).

Discussion

Data collected by the quality control system of the Belgian healthcare system enabled the study of a large, real-world population of well-characterised people living with type 1 diabetes. Over the last 20 years, we have observed an improvement in glycaemic control and LDL-cholesterol levels, but an increase in the prevalence of overweight, obesity and combined metabolic abnormalities in people living with type 1 diabetes.

Table 3 Comparison of the prevalence of metabolic health indicators, complications and treatments in people living with type 1 diabetes with or without combined metabolic abnormalities (defined by the WHO definition of the metabolic syndrome/combined metabolic abnormalities, without albuminuria), stratified by sex (2022 data)

	Men			Women		
Presence of combined metabolic abnormalities	No	Yes	*p* value	No	Yes	*p* value
Number of patients	862	835		767	525	
Metabolic health indicators						
Smoker[a]	187 (22.7) (*N*=822)	168 (20.9) (*N*=804)	ns	109 (15.2) (*N*=715)	84 (16.6) (*N*=507)	ns
HbA_{1c} >58 mmol/mol (>7.5%)	318 (36.9)	408 (48.9)	<0.0001	315 (41.1)	280 (53.3)	<0.0001
BMI >30 kg/m^2[b]	35 (4.1)	320 (38.3)	<0.0001	61 (8.0)	232 (44.2)	<0.0001
Hypertension[b]	185 (21.5)	734 (87.9)	<0.0001	132 (17.2)	448 (85.3)	<0.0001
Dyslipidaemia[b]	197 (22.9)	730 (87.4)	<0.0001	138 (18.0)	437 (83.2)	<0.0001
TG ≥1.7 mmol/l[b]	57 (6.6)	230 (27.5)	<0.0001	43 (5.6)	123 (23.4)	<0.0001
$eGDR_{WC}$[a]	8.1 ± 1.8 (*N*=291)	4.5 ± 1.8 (*N*=305)	<0.0001	8.6 ± 1.9 (*N*= 257)	5.2 ± 1.9 (*N*=175)	<0.0001
$eGDR_{BMI}$	8.3 ± 1.7	5.2 ± 1.5	<0.0001	8.4 ± 1.6	5.2 ± 1.7	<0.0001
Complications[c]						
Eye complications	208 (29.0 [25.4, 32.8]) (*N*=838)	444 (44.8 [40.7, 48.9] (*N*=819)	<0.0001	184 (27.6 [24.0, 31.6] (*N*=743)	268 (41.7 [36.6, 47.0]) (*N*=493)	<0.0001
Peripheral neuropathy	26 (4.6 [3.1, 6.7]) (*N*=602)	103 (10.6 [8.2, 13.6]) (*N*=602)	<0.001	32 (6.3 [4.5, 8.8]) (*N*=548)	68 (12.6 [9.2, 17.0]) (*N*=374)	<0.01
Chronic kidney disease	39 (8.6 [6.3, 11.6]) (*N*=502)	131 (14.4 [11.6, 17.7]) (*N*=631)	<0.01	40 (7.8 [5.7, 10.5]) (*N*=536)	116 (16.8 [13.1, 21.3]) (*N*=435)	<0.0001
CVD	29 (4.8 [3.2, 7.1]) (*N*=544)	111 (8.6 [6.3, 11.7]) (*N*=561)	<0.01	24 (4.1 [2.7, 6.3]) (*N*=516)	67 (9.1 [6.4, 12.8]) (*N*=342)	<0.01
Treatment						
Glucose-lowering drugs						
CSII[a]	133 (15.8) (*N*=842)	104 (12.7) (*N*=816)	ns	225 (29.8) (*N*=755)	115 (22.1) (*N*=520)	<0.01
Metformin[a]	43 (5.0) (*N*=859)	145 (17.5) (*N*=830)	<0.0001	45 (5.9) (*N*=762)	91 (17.5) (*N*=519)	<0.0001
Cardiovascular drugs						
Lipid-lowering drugs[b]	188 (21.8)	700 (83.8)	<0.0001	130 (16.9)	420 (80.0)	<0.0001
Antihypertensive drugs[b]	84 (9.7)	573 (68.6)	<0.0001	82 (10.7)	354 (67.4)	<0.0001
SGLT2 inhibitors[a]	11 (1.3) (*N*=855)	38 (4.6) (*N*=824)	<0.001	14 (1.8) (*N*=764)	14 (2.7) (*N*=518)	ns
GLP1 receptor agonists[a]	3 (0.3) (*N*=858)	25 (3.0) (*N*=824)	<0.001	19 (2.5) (*N*=766)	31 (6.0) (*N*=518)	<0.01

Values are *n* (%) for categorical variables and mean ± SD for continuous variables

Hypertension is defined as BP ≥140/90 mmHg and/or treatment with antihypertensive drugs, dyslipidaemia is defined as HDL-cholesterol <0.9 mmol/l (<35 mg/dl) in men (<1 mmol/l (<40 mg/dl) in women) and/or treatment with lipid-lowering drugs. Eye complications is defined as ever been treated (laser photocoagulation and/or intravitreal injection) for diabetic retinopathy or diabetic maculopathy, or the presence of diabetic retinopathy (proliferative or non-proliferative) or blindness. Peripheral neuropathy is defined as an abnormal sensitivity test or treatment for peripheral neuropathy. Chronic kidney disease is defined as eGFR <60 ml/min per 1.73 m^2 (Modification of Diet in Renal Disease study equation [40]). CVD is defined as the presence of myocardial infarction, heart attack, coronary revascularisation (percutaneous coronary intervention or coronary artery bypass grafting), carotid revascularisation, heart failure, absence of foot pulses or peripheral bypass surgery. Lipid-lowering therapy is defined as use of statins, fibrates or ezetimibe. Antihypertensive therapy is defined as the use of either ACE inhibitors (including sartans) or other antihypertensive drugs

[a]Only known for the indicated population (*N*)

[b]Parameters included in the definition of the metabolic syndrome/combined metabolic abnormalities

[c]The prevalence of complications was analysed using the GEE model, adjusted for age and diabetes duration, presented as *n* (% [95% CI])

N, population size; *n*, number of observations; ns, not significant

In recent decades, the prevalence of obesity in the general population has increased, mainly due to the adoption of a progressively more sedentary lifestyle and the consumption of less healthy diets [21, 22]. In Belgium, age-adjusted obesity has increased from 11.5% in men and 11.1% in women in 1997 to 16.4% in men and 14.5% in women in 2018 [23]. In the current study, we show that the proportion of obesity in adults with type 1 diabetes in Belgium doubled from 12% in 2001 to 22% in 2022, confirming the finding that obesity is a growing emergency in people living with type 1 diabetes [4, 5, 22, 24–26].

The presence of a combination of metabolic abnormalities, such as central obesity, insulin resistance, dyslipidaemia and hypertension, often referred to as the metabolic syndrome or combined metabolic abnormalities, increases the risk of CVD in the general population as well as in people living with type 2 diabetes [9, 16, 27]. The prevalence of combined metabolic abnormalities ranges from 20–50% in the general adult population [6, 10, 28], but reaches almost 80% in people living with type 2 diabetes [6, 28]. An international review by Belete et al reported a pooled prevalence of combined metabolic abnormalities of 25.9% (95% CI 20.5, 31.6) in women and 22.5% (95% CI 16.7, 28.9) in men living with type 1 diabetes (studies performed between 2005 and 2020), with rates varying widely depending on patient characteristics and definition used [28]. Time-based subgroup analyses revealed a higher prevalence of combined metabolic abnormalities in the studies performed between 2015 and 2020 (26.6%) compared with those performed between 2005 and 2014 (21.8%) [28].

In the present study, we confirmed an increasing prevalence of combined metabolic abnormalities in adults living with type 1 diabetes, corrected for age and diabetes duration, irrespectively of the definition used. In 2001, combined metabolic abnormalities were identified in 27.5% of women and 31.7% of men, according to the WHO definition. In 2022, these proportions increased to 40.2% and 49.7% in women ($p<0.01$) and men ($p<0.0001$), respectively. The WHO definition of the metabolic syndrome/combined metabolic abnormalities includes microalbuminuria as a criterion, reflecting the pathophysiology of albuminuria seen in patients with type 2 diabetes, which may lead to a higher prevalence of combined metabolic abnormalities compared with other definitions. However, as albuminuria in people living with type 1 diabetes is typically a microvascular complication, indicating the early stages of renal disease, we repeated the analysis using the WHO definition of the metabolic syndrome/combined metabolic abnormalities without microalbuminuria. The increase in the prevalence of combined metabolic abnormalities remained when albuminuria was removed from the definition (from 21.8% in 2001 to 38.2% in 2022 in women [$p<0.0001$] and from 24.7% in 2001 to 46.4% in 2022 in men [$p<0.0001$]).

In our study, an increase in the prevalence of combined metabolic abnormalities was also observed when using the NCEP-ATPIII and IDF definitions of the metabolic syndrome/combined metabolic abnormalities, which use WC as the key obesity measure [28], but the overall prevalence was higher compared with the WHO definitions of the metabolic syndrome/combined metabolic abnormalities (with and without albuminuria). This may be due to the fact that WC data were only available from 2005 onwards and only for a minority of participants, although the small differences in threshold values for hypertension and HDL-cholesterol between definitions may also have had an effect. A recent Belgian study reported a prevalence of combined metabolic abnormalities in people living with type 1 diabetes of 30% according to the NCEP-ATPIII definition (data collected between 2018 and 2022) [29].

We have shown previously that, in people living with type 1 diabetes, glycaemic and lipid control improved over time due to a combination of provision of technology, education and quality monitoring [14]. HbA_{1c} and LDL-cholesterol levels also decreased over time in the present study in people living with type 1 diabetes. Rates of lipid-lowering and antihypertensive therapy increased, which may be at least partially explained by the European Association for the Study of Diabetes and the American Diabetes Association consensus guidelines recommending more routinely cardiovascular treatment in addition to glucose-lowering treatment in people living with diabetes. As a result, the proportions of people being treated with lipid-lowering or antihypertensive drugs and thus by definition being identified as having dyslipidaemia or hypertension strongly increased, as did the number of people with combined metabolic abnormalities. However, disturbingly, obesity and central obesity became more prevalent with the decrease in HbA_{1c}.

Those with combined metabolic abnormalities had higher glucose levels (HbA_{1c} >58 mmol/mol or >7.5%) and (as per definition) more overweight and hypertension and worse lipid control compared to those without combined metabolic abnormalities. Our results are in line with the findings of Lee et al [10]. In their study, people with combined metabolic abnormalities had higher glucose levels (HbA_{1c} of 68 mmol [8.4%] vs 64 mmol [8.0%]) and a significantly higher prevalence of hypertension (89% vs 29%), dyslipidaemia (combined elevated TG levels and lower HDL-cholesterol levels, 50% vs 9.1%) and obesity (50% vs 7.2%) compared to those without combined metabolic abnormalities. In our population, despite higher use of statins and antihypertensive drugs in those with combined metabolic abnormalities, approximately one-fifth of individuals with combined metabolic abnormalities were not on statins. In addition, one-fifth of those with combined

metabolic abnormalities smoked, further accelerating the risk of micro- and macrovascular complications in this population.

We found a strong relationship between combined metabolic abnormalities and the prevalence of CVD, but also eye complications, peripheral neuropathy and chronic kidney disease, corrected for age, diabetes duration and HbA_{1c}. This finding is in line with some previous observations, depending on the definition of the metabolic syndrome/combined metabolic abnormalities used, and highlights the importance of identification of combined metabolic abnormalities and initiation of more aggressive therapeutic approaches in these patients [10, 12, 22, 30].

Our data show that people with combined metabolic abnormalities are less often treated with CSII. The maximum insulin storage capacity of insulin pumps may have influenced treatment decisions for individuals with combined metabolic abnormalities, especially those with higher body weight. However, no patch pumps for which the maximum insulin storage capacity could be a major issue were available in Belgium over the time period of data collection.

In our population, people with combined metabolic abnormalities are more often treated with adjunct therapies such as metformin, SGLT2 inhibitors and GLP1 receptor agonists. Metformin is the most commonly used treatment to increase insulin sensitivity in insulin-resistant conditions. It decreases hepatic glucose production and enhances insulin-stimulated glucose disposal in peripheral tissues [22, 31]. Metformin is an inexpensive and well-established oral glucose-lowering drug, and the first-line treatment in patients with type 2 diabetes. It is frequently used as an adjunct to intensive insulin therapy in people living with type 1 diabetes [32, 33]. It has been shown to have some benefit in reducing insulin doses and weight, although no long-term beneficial effects were observed when patients were followed for 10 years [34]. The recent international study 'REducing with Metformin Vascular Adverse Lesions' (REMOVAL) suggests a reduction in cardiovascular risk as a result of metformin use in people with long-standing type 1 diabetes [35]. However, in most countries, including Belgium, there is no official indication for use of metformin in patients with type 1 diabetes. Nevertheless, 11% of our type 1 diabetes population used metformin as an adjunct therapy (2022 data), in line with 8–15% of the population reported in Scotland (2016 data) [35] and 4–7% of the population in the USA (T1D Exchange Registry, 2016–2018 data) [26].

As SGLT2 inhibitors and GLP1 receptor agonists are intended for use in people living with type 2 diabetes, use of these drugs for treatment of people living with type 1 diabetes is rare and they are prescribed on an individual basis. SGLT2 inhibitors reduce blood glucose levels by decreasing the resorption of glucose in the kidneys, and exert nephroprotective and cardioprotective effects [22]. Studies of the use of SGLT2 inhibitors in people living with type 1 diabetes have shown a positive effect on BMI and daily insulin dose, but warn of a potential increased risk of euglycaemic ketoacidosis [4, 36]. While further research is needed on the potential cardiorenal benefits of use of SGLT2 inhibitors in people with type 1 diabetes, for the moment it may be advisable to prescribe them only to compliant patients with a BMI greater than 27 kg/m^2, and to interrupt their use in cases of insulin dose reduction and dehydration [37, 38]. GLP1 receptor agonists enhance insulin secretion in a glucose-dependent manner, inhibit the release of glucagon, promote satiety and slow down gastric emptying. In addition to their glucose-lowering effect, GLP1 receptor agonists have a positive effect on BMI and cardiovascular events [4, 22, 39]. Due to their safety profile and demonstrated positive effect on obesity and insulin resistance in people living with type 1 diabetes, these drugs may be used as an adjunct therapy in such patients [39].

Despite important strengths, such as the size and quality of the database as well as the duration of observation, our study has limitations. The cross-sectional nature of the data does not allow individual longitudinal follow-up or investigation of causality. Also, the lack of information on physical activity, ethnicity or socioeconomic status is a weakness.

Conclusion People living with type 1 diabetes are increasingly affected by overweight, obesity and combined metabolic abnormalities. This co-occurrence of diseases may result in a further elevated risk of microvascular and macrovascular complications. Early identification of the presence of combined metabolic abnormalities should enable therapeutic interventions to be modified towards multifactorial approaches, with attention to education on avoidance of overweight (e.g. dietary counselling) in addition to strict glycaemic control and intensification of use of antihypertensive drugs and statins. The use of adjunct therapies deserve to be explored more thoroughly in this population as a tool to reduce the risk of complications.

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Data availability Data cannot be shared publicly because of the use of pseudonymised person-level data. Readers who wish to access some or all of the data require approval from the Belgian Information Security Committee on Social Security and Health. More information about the access procedure may be obtained by contacting iqed@sciensano.be.

Metadata (e.g. overview of variables, legal framework) are available on https://fair.healthdata.be/.

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