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Public health burden of pre-diabetes and diabetes in Luxembourg: finding from the 2013–2015 European Health Examination Survey

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ABSTRACT

Objective The aim of this study was to determine the burden and risk factors of prediabetes and diabetes in the general adult population of Luxembourg.

Design Cross-sectional survey between 2013 and 2015.

Setting Data were collected as part of the European Health Examination Survey in Luxembourg (EHES-LUX).

Participants 1451 individuals were recruited in a random sample of the 25–64-year-old population of Luxembourg.

Outcomes Diabetes was defined by a glycaemic biomarker (fasting plasma glucose (FPG) ≥7.0 mmol/L), self-reported medication and medical diagnosis; prediabetes by a glycaemic biomarker (FPG 5.6–6.9 mmol/L), no self-reported medication and no medical diagnosis. Undiagnosed diabetes was defined only from the glycaemic biomarker; the difference between total and undiagnosed diabetes was defined as diagnosed diabetes. Odds of diabetes and prediabetes as well as associated risk factors were estimated.

Results The weighted prevalence of prediabetes and diabetes was 25.6% and 6.5%, respectively. Nearly 4.8% (men: 5.8%; women: 3.8%) were diagnosed diabetes and 1.7% (men: 2.6%; women: 0.7%) were undiagnosed diabetes. The multivariable-adjusted OR (MVOR) for diabetes risk were: age 1.05 (95% CI 1.01 to 1.09), family history of diabetes 3.24 (1.95–5.38), abdominal obesity 2.63 (1.53–4.52), hypertension 3.18 (1.76–5.72), one-unit increase of triglycerides 1.16 (1.10–1.22) and total cholesterol 0.74 (0.64–0.86). The MVOR for prediabetes risk were: age 1.04 (95% CI 1.02 to 1.06), male sex 1.84 (1.30–2.60), moderate alcohol consumption 1.38 (1.01–1.89), family history of diabetes 1.52 (1.13–2.05), abdominal obesity 1.44 (1.06–1.97), second-generation immigrants 0.61 (0.39–0.95) and a one-unit increase of serum high-density lipoprotein cholesterol 0.70 (0.54–0.90).

Conclusions In Luxembourg, an unexpectedly high number of adults may be affected by prediabetes and diabetes. Therefore, these conditions should be addressed as a public health priority for the country, requiring measures for enhanced detection and surveillance, which are currently lacking, especially in primary care settings.

Strengths and limitations of this study

- ► Diagnosis of diabetes were determined from several sources (ie, glycaemic biomarker, self-reported medication and medical diagnosis).
- ► Diagnosed and undiagnosed diabetes were differentiated.
- ► Two different glycaemic biomarkers were studied (ie, fasting plasma glucose and glycated haemoglobin).
- ► A low participation rate was observed, but there were no differences between the randomly selected sample initially contacted to participate in the survey (n=6396) and the real respondents' sample (n=1451).
- ► An upper age limit of 65 years leads to an underestimation of diabetes prevalence.

INTRODUCTION

Diabetes is one of the most prevalent chronic disease in the world affecting 422 million adults in 2014[1] and its societal burden has been increasing over time due to population ageing and high prevalence of underlying risk factors.

Despite the knowledge and efforts to tackle this condition, the number of people with undiagnosed diabetes still remains high all around the world.[2] Identification, follow-up and treatment of affected individuals are necessary to prevent and reduce complications (retinopathy, neuropathy, etc).[3]

Prediabetes is an intermediate status between normal glucose and frank diabetes.[4] Individuals with prediabetes are more likely to develop diabetes (approximately 5%–10% within 1 year) than normoglycaemic individuals.[4–6] Targeted interventions in individuals with prediabetes may prevent progression to the disease, as demonstrated in the Diabetes Prevention Programme.[7] This progression has public health relevance given the societal and economic burden of both prediabetes and diabetes and their associated comorbidities in the context of ageing populations across many countries worldwide.[8]

Several studies have investigated the prevalence and potential risk factors of diabetes,[9] prediabetes[9 10] and undiagnosed diabetes,[9 11 12] revealing the role of sociodemographic factors, genetics, adiposity, blood lipids and lifestyles but also with conflicting results between studies. This discrepancy may be based on the age of the studied population,[10] the interdependence between explanatory variables or the sociocultural differences between countries.[9 13] Some national population-based studies in Western European countries have reported on diabetes prevalence and its associated factors, although with limited attention to prediabetes.[11 14] In Luxembourg, very few population-based studies have investigated diabetes prevalence and potential risk factors.[15–17] To our knowledge, no study to date has specifically focused on undiagnosed diabetes and prediabetes. Therefore, the aims of this study were to provide current estimates of prediabetes and diabetes prevalence in Luxembourg, as well as examine associated risk factors using data from the most recent European Health Examination Survey (EHES).

METHODS

Study design

Data were collected as part of the EHES in Luxembourg (EHES-LUX), a 2013–2015 cross-sectional survey in a randomly selected representative sample of the general adult population. A detailed description of the study protocol has been previously published.[18–21] Briefly, 1529 residents aged 25–64 years participated in this study, representing a response rate of 26.7%.[19] Among them, 21 pregnant women were removed from the study. Additionally, 57 participants without any information on their prediabetes status (no available glycaemic biomarker data for these individuals) were also excluded from the analyses. A total of 1451 participants with complete information on their glycaemic status were included in the present study.

Diabetes classification

In order to categorise all diagnosed and undiagnosed cases in our survey, diabetes was defined according to at least one of these three criteria: a fasting plasma glucose (FPG) greater or equal to 7.0 mmol/L, a self-reported physician diagnosis of diabetes and/or use of glucose-lowering medications. Undiagnosed diabetes was defined as an FPG greater or equal to 7.0 mmol/L. Diagnosed diabetes was defined as the difference between total and undiagnosed diabetes. For comparisons with US-based studies, prediabetes was defined by 5.6 mmol/L <FPG < 7.0 mmol/L (based on the American Diabetes Association (ADA)[22] and no self-reported physician diagnosis of diabetes or self-report of any diabetes medication. Normoglycaemia was defined by FPG <5.6 mmol/L and no physician diagnosis of diabetes or self-report of glucose-lowering drugs.

Diabetes was also defined by the glycated haemoglobin (HbA1c) level. According to ADA guidelines, HbA1c thresholds of prediabetes are 5.7%–6.4% (1.18-1.40 g/L) while diabetes is defined as an HbA1c level ≥6.5% (1.41 g/L).[22] HbA1c was used for sensitivity analysis (Venn diagram).

Biochemical variables

After an overnight 8-hour fast, a venous blood sample was drawn from the arm of each subject in sitting position by antecubital vein puncture. The blood samples were transferred to a national laboratory using strict internal and external standard quality control techniques. After extraction and centrifugation, they were immediately analysed. The laboratory tests concerned FPG, HbA1c, triglycerides, serum total cholesterol and serum high-density lipoprotein (HDL) cholesterol.

Other model variables

Several questions related to family history of diabetes (father, mother or brother/sister) were used to complete information on individuals' diabetes. As previously described,[19] additional information on demographics (including immigration status classified by 'no immigrant', 'first generation' and 'second generation'), lifestyle factors (including alcohol consumption, categorised from a threshold of two or three drinks/day according to participants' sex and corresponding to WHO recommendations[23]), anthropometric measures and health status variables were collected as part of the EHES protocol.

Statistical methods

Overall prevalences estimates and prevalences according to sex and age were calculated from weighted statistical methods to produce nationally representative estimates using population census data of Luxembourg in 2011. Sampling weights were computed from the probabilities to be selected at each stage of sampling and were adjusted for non-response. Then they were assigned to each participant from the same stratum. To be comparable, prevalence rates from Luxembourg and other countries were age-standardised or even age-standardised and sex-standardised when data were available (WHO 2000–2025 World Standard Population).

Descriptive statistics of correlates and related comorbidities of diabetes statuses were calculated. As continuous variables did not contain any extreme values, mean and SD were used. To evaluate the association between glycaemic status and sample characteristics, two-sample Student's t-tests were used. Regarding categorical variables, if the expected values in any of the cells of a contingency table were not below 5, Pearson's χ^2 tests were used. Otherwise, a Fisher's exact test was preferred.

Logistic regression analyses adjusted for sex, age, region of residence and body mass index (BMI) were used to analyse the factors associated with diabetes in comparison with no diabetes, then the factors associated with prediabetes versus normoglycaemia. In each case, multivariable-adjusted OR (MVOR) and 95% CI were estimated. Interactions between sex and the other covariates on study outcomes did not yield significance in our main analysis and thus were not included in the regression models. In case of multicollinearity between explanatory variables (abdominal obesity and BMI), the most strongly associated variable with the outcome of interest in univariate analyses was kept. Selection of variables was also based on previous literature. Then, to avoid missing possible covariates associated with the outcome of multivariable analyses, a wide p<0.20 criterion measured in univariate analyses was used to select covariates to be included in the adjusted models. Non-selected variables were discarded from the final model.

All statistical analyses were carried out using SAS V.9.4 (SAS Institute, Cary, North Carolina, USA). A two-sided p<0.05 was considered statistically significant in descriptive and multivariate analyses.

Patient and public involvement

No patients were involved in setting the research question, nor were they involved in the planning of the study. At the end of the study, the participant received by regular post the results of biological tests (blood and urine) and the results of medical examinations. A copy was sent, if wanted/requested, to his/her medical doctor (general practitioner, family doctor or any referent medical doctor). Results of the biological analysis and medical examinations were validated and evaluated by the clinical committee who verified the presence or absence of anomalies. In case of abnormal results, the participant was informed in the abovementioned postal letter. In case of severe/highly abnormal results, the laboratory or the clinical committee informed the study nurse coordinator or a back-up study nurse. The participant was then contacted by phone in order to invite him/her to consult his/her medical doctor, which has been concluded with a follow-up call.

RESULTS

The prevalence of diabetes (including undiagnosed and diagnosed cases) weighted on sex, age and region was 6.5% (8.4% for men and 4.5% for women) including 1.7% of undiagnosed diabetes cases (2.6% for men and 0.7% for women), as described in table 1. A quarter (25.6%) of Luxembourg residents were categorised as subjects with prediabetes (33.1% for men and 17.6% for women). Prediabetes prevalence increased with age regardless of gender. Moreover, diabetes prevalence regularly increased with age in men.

The Venn diagram for diabetes using this classification is shown in figure 1. We noticed that among participants with diabetes, almost 75% of individuals met both FPG and HbA1c criteria, 11.2% met only HbA1c criterion and 15.9% met only FPG criterion.

The association between several explanatory variables and glycaemic status is described in table 2. Sex was strongly associated with glycaemic status (p<0.01) with less normoglycaemic men than women, but not with diabetes awareness (diagnosed compared with undiagnosed diabetes; p=0.09). Age and BMI were also associated with glycaemic status (respectively p<0.01 and p<0.01); individuals with diabetes were more likely to be older and with a higher BMI; but age and BMI were not associated with diabetes awareness (respectively p=0.97 and p=0.58). Similar associations were observed with socioeconomic factors: education was significantly associated with glycaemic status (p<0.01) with a higher proportion of diabetes in participants with primary education but not with diabetes awareness (p=0.96), similarly for job status (respectively p=0.01 and p=0.24) where the proportion of diabetes was higher in not-working participants.

Table 1 Weighted prevalence of 25–64-year-old prediabetes, undiagnosed and diagnosed diabetes, with 95% CI (n=1451)

	Normoglycaemia	Prediabetes	Diagnosed diabetes	Undiagnosed diabetes
Overall (n=1.431)	68.0 (65.5–70.4)	25.6 (23.3–27.9)	4.8 (3.7–5.9)	1.7 (1.0–2.3)
Male (n=695)	58.5 (54.7–62.2)	33.1 (29.6–36.7)	5.8 (4.0–7.5)	2.6 (1.4–3.8)
25–34 (n=125)	76.3 (68.7–83.8)	22.9 (15.4–30.4)	0.8 (0.0–2.5)	/
35–44 (n=214)	64.0 (57.5–70.6)	31.2 (24.8–37.5)	2.1 (0.2–4.0)	2.7 (0.5–4.9)
45–54 (n=223)	53.0 (46.3–59.7)	35.9 (29.5–42.4)	7.4 (3.9–10.8)	3.7 (1.1–6.2)
55–64 (n=133)	37.4 (28.9–45.8)	44.1 (35.5–52.7)	14.5 (8.5–20.5)	4.0 (0.5–7.5)
Female (n=756)	77.9 (74.9–80.9)	17.6 (14.8–20.3)	3.8 (2.4–5.2)	0.7 (0.1–1.2)
25–34 (n=156)	88.1 (82.8–93.3)	8.6 (4.1–13.1)	3.3 (0.4–6.2)	/
35–44 (n=226)	85.4 (80.8–90.1)	12.4 (8.0–16.8)	2.1 (0.2–4.0)	/
45–54 (n=221)	75.0 (69.1–80.9)	21.5 (15.9–27.0)	3.0 (0.6–5.4)	0.5 (0.0–1.5)
55–64 (n=153)	58.8 (50.9–66.7)	30.6 (23.2–38.0)	8.0 (3.6–12.4)	2.6 (0.0–5.2)

Data are % (95% CI).

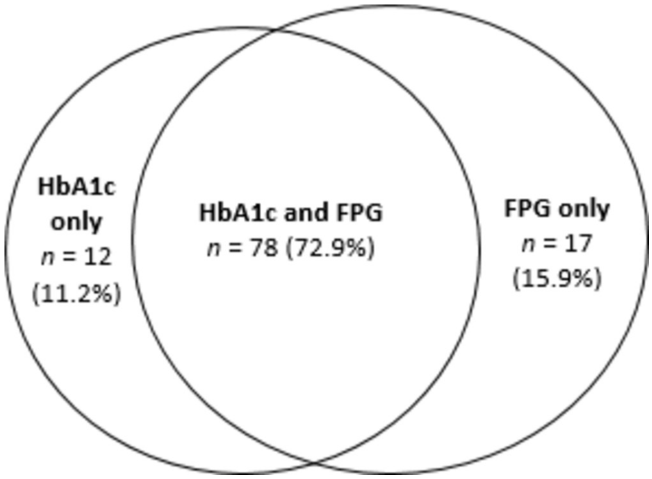

Figure 1 Venn diagram for individuals' diabetes (fasting plasma glucose (FPG) versus glycated haemoglobin (HbA1c)), according to the American Diabetes Association classification.

The factors associated with diabetes compared with no diabetes and then those variables associated with prediabetes compared with no diabetes are presented in table 3. Total cholesterol (MVOR=0.74 for a one-unit increase, 95% CI 0.64 to 0.86) was associated with a lower likelihood of diabetes, whereas age (MVOR=1.05, 1.01 to 1.09), family history of diabetes (MVOR=3.24, 1.95 to 5.38), abdominal obesity (MVOR=2.63, 1.53 to 4.52), hypertension (MVOR=3.18, 1.76 to 5.72) and triglycerides (MVOR=1.16 for a one-unit increase, 1.10 to 1.22) were all associated with a higher likelihood of diabetes.

When we compared prediabetes to no diabetes, second-generation immigrants (MVOR=0.61, 95% CI 0.39 to 0.95) and HDL cholesterol (MVOR=0.70 for a one-unit increase, 0.54 to 0.90) were associated with a lower likelihood of prediabetes, whereas age (MVOR=1.04, 1.02 to 1.06), male sex (MVOR=1.84, 1.30 to 2.60), the consumption of two or three units or less per day of alcohol (MVOR=1.38, 1.01 to 1.89), family history of diabetes (MVOR=1.52, 1.13 to 2.05) and abdominal obesity (MVOR=1.44, 1.06 to 1.97) were associated with a higher likelihood of prediabetes.

DISCUSSION

Prevalence estimates

Data from the EHES-LUX survey provide current national prevalence estimates of diabetes, including undiagnosed diabetes and for the first time prediabetes in a representative population sample of adults in Luxembourg.[19] Using WHO standardisation, the overall standardised diabetes prevalence was 5.8% among 25–64-year-old adults (men: 7.5%; women: 4.1%), of which undiagnosed diabetes prevalence was 1.4% (men: 2.3%; women: 0.6%). Among participants with diabetes, 23.8% of them were unaware of their condition. Compared with previous estimates of diabetes prevalence in Luxembourg from the nationwide Observation of Cardiovascular Risk Factors in Luxembourg (ORISCAV-LUX) study conducted in 2007–2009,[15] a great increase was observed for both sexes (respectively 7.5% vs 4.4% for men; 4.1% vs 3.0% for women). In this previous cross-sectional study, among 18–69-year-old adults, the criteria to define diabetes status were based on glucose-lowering medication and/or an FPG≥7.0 mmol/L, and not also from a physician diagnosis as in our study. Using the ORISCAV-LUX diabetes definition, the EHES prevalence would be about 1.0 point less. It remains a 10% difference for women and a 64% difference for men between the two studies.

Earlier findings from the Diabecolux study, based on exhaustive data from the national health insurance registry,[17] revealed a 3.0% (men: 3.6%; women: 2.5%) 25–64 standardised prevalence of treated diabetes in 2006 in Luxembourg. The main methodological difference on prevalence estimates between Diabecolux and EHES studies concerns the diabetes status definition: undiagnosed patients and patients with untreated diabetes were missing in Diabecolux study. But, if we only consider treated patients, age-standardised prevalence differences between EHES and Diabecolux remain remarkable. Indeed, there is still a striking 40%-increase for men and women in treated diabetes prevalence in 8 years, which is worrisome given the short time interval. These comparisons (with ORISCAV-LUX and Diabecolux) are in line with international data.[1 24] The observed increase in diabetes prevalence in Luxembourg is likely to be explained by demographic and lifestyle changes (population ageing, more sedentary behaviours, overnutrition and increasing obesity prevalence).[1]

As prediabetes is a high-risk state for developing diabetes, the surveillance of this population is a major public health priority. The present study provides the first nationwide estimate of prediabetes prevalence. Results are alarming showing that 25% of adults in Luxembourg might suffer from this condition, with an even higher prevalence of prediabetes among male participants. Prediabetes prevalence varies according to Impaired fasting glucose (IFG) definitions[25] and individuals' age.[5] Hence, in order to compare prevalence between studies,[10–15 26–28] it was necessary to harmonise prediabetes definitions and age categories observed in the literature using the same prediabetes definitions. Prevalence comparison shows that in Luxembourg, prediabetes prevalence estimates are similar or slightly lower than those in England,[10 11] similar to Northeast Germany[28] or South Korean values,[13] but much higher than those reported in a neighbouring country as France[14] or South Germany,[28] and even slightly higher than estimates in the USA.[27]

The comparison of Luxembourg diabetes prevalence with other European or non-European national prevalences revealed, for instance, higher diagnosed values[26] in Germany, but lower estimates in France[14] despite a slightly older population than the EHES-LUX sample, lower estimates in England,[11 12] similar estimates in South Korea[13] but higher in the USA.[27] The timeframe of Pierce *et al* and Kim *et al*'s studies and the participants' age in the

Table 2 Descriptive characteristics of the EHES-LUX sample by glycaemic status

		Normoglycaemia	Prediabetes	Diabetes	P	Diagnosed diabetes	Undiagnosed diabetes	P
	n	n=986	n=370	n=95	value*	n=71	n=24	value†
Age (years)	1451	43.4±9.7	48.3±9.7	51.6±9.4	<0.01	51.5±9.8	51.6±8.3	0.97
Sex					<0.01			0.09
Men	695	398 (57.3%)	235 (33.8%)	62 (8.9%)		43 (69.3%)	19 (30.7%)	
Women	756	588 (77.8%)	135 (17.9%)	33 (4.4%)		28 (84.8%)	5 (15.2%)	
Marital status					0.36			0.02
Married	958	639 (66.7%)	254 (26.5%)	65 (6.8%)		18 (60.0%)	12 (40.0%)	
Not married	493	347 (70.4%)	116 (23.5%)	30 (6.1%)		53 (81.5%)	12 (18.5%)	
Education					<0.01			0.96
Primary	364	217 (59.6%)	110 (30.2%)	37 (10.2%)		27 (73.0%)	10 (22.9%)	
Secondary	553	370 (66.9%)	147 (26.6%)	36 (6.5%)		27 (75.0%)	9 (25.0%)	
Tertiary	529	396 (74.9%)	112 (21.2%)	21 (4.0%)		16 (76.2%)	5 (23.8%)	
Job status					0.01			0.24
Not working	341	213 (62.5%)	95 (27.9%)	33 (9.7%)		27 (81.8%)	6 (18.2%)	
Working	1109	772 (69.6%)	275 (24.8%)	62 (5.6%)		44 (71.0%)	18 (29.0%)	
Immigrant origin					0.14			0.86
Not immigrant	527	349 (66.2%)	151 (28.7%)	27 (5.1%)		21 (77.8%)	6 (22.2%)	
First-generation immigrant	691	470 (68.0%)	171 (24.8%)	50 (7.2%)		37 (74.0%)	13 (26.0%)	
Second-generation immigrant	227	162 (71.4%)	48 (21.1%)	17 (7.5%)		12 (70.6%)	5 (29.4%)	
Alcohol (last year)					<0.01			<0.01
No drinker	581	433 (74.5%)	114 (19.6%)	34 (5.9%)		32 (94.1%)	2 (5.9%)	
Two or three units per day or less	793	513 (64.7%)	232 (29.3%)	48 (6.0%)		30 (62.5%)	18 (37.5%)	
More than two or three units per day	74	38 (51.3%)	24 (32.4%)	12 (16.2%)		9 (75.0%)	3 (25.0%)	
Smoking					<0.01			0.37
Never	795	581 (73.1%)	171 (21.5%)	43 (5.4%)		32 (74.4%)	11 (25.6%)	
Currently	326	207 (63.5%)	94 (28.8%)	25 (7.7%)		17 (68.0%)	8 (32.0%)	
Ex-smokers	327	196 (59.9%)	105 (32.1%)	26 (7.9%)		22 (84.6%)	4 (15.4%)	
Diabetes family history					<0.01			0.72
No	1028	738 (71.8%)	244 (23.7%)	46 (4.5%)		34 (73.9%)	12 (26.1%)	
Yes	421	247 (58.7%)	126 (29.9%)	48 (11.4%)		37 (77.1%)	11 (22.9%)	
WRPA					0.01			0.74
Mostly WRPA	425	284 (66.8%)	111 (26.1%)	30 (7.1%)		23 (76.7%)	7 (23.3%)	
No mostly WRPA	744	531 (71.4%)	174 (23.4%)	39 (5.2%)		28 (71.8%)	11 (28.2%)	
Not working	279	169 (60.6%)	85 (30.5%)	25 (8.9%)		20 (80.0%)	5 (20.0%)	
APA					<0.01			0.72
< 150 min per week	542	402 (74.2%)	117 (21.6%)	23 (4.2%)		18 (78.3%)	5 (21.7%)	
≥ 150 min per week	906	583 (64.3%)	252 (27.8%)	71 (7.8%)		53 (74.7%)	18 (25.3%)	
MSPA					<0.01			0.96
<2 days per week	297	226 (76.1%)	59 (19.9%)	12 (4.0%)		9 (75.0%)	3 (25.0%)	
≥2 days per week	1151	759 (65.9%)	310 (26.9%)	82 (7.1%)		62 (75.6%)	20 (24.4%)	
BMI (kg/m^2)	1449	25.5±4.4	28.1±4.9	31.4±6.6	<0.01	31.1±6.6	32.0±6.8	0.58
Abdominal obesity								
No	969	720 (74.3%)	218 (22.5%)	31 (3.2%)	<0.01	24 (77.4%)	7 (22.6%)	0.67
Yes	482	266 (27.0%)	152 (41.1%)	64 (13.3%)		47 (73.4%)	17 (26.6%)	
Depressive symptoms								
No	1142	773 (67.7%)	303 (26.5%)	66 (5.8%)	0.04	49 (74.2%)	17 (25.8%)	0.65
Yes	307	212 (69.1%)	67 (21.8%)	28 (9.1%)		22 (78.6%)	6 (21.4%)	

Continued

Table 2 Continued

	n	Normoglycaemia n=986	Prediabetes n=370	Diabetes n=95	P value*	Diagnosed diabetes n=71	Undiagnosed diabetes n=24	P value†
Hypertension					<0.01			0.86
No	995	750 (75.4%)	220 (22.1%)	25 (2.5%)		19 (76.0%)	6 (24.0%)	
Yes	454	235 (51.8%)	149 (32.8%)	70 (15.4%)		52 (74.3%)	18 (25.7%)	
Health perception					<0.01			0.32
Good or very good	1110	773 (69.6%)	284 (25.6%)	53 (4.8%)		38 (71.7%)	15 (28.3%)	
Fair, bad or very bad	340	213 (62.6%)	86 (25.3%)	41 (12.1%)		33 (80.5%)	8 (19.5%)	
HDL (mmol/L)	1448	3.0±0.8	2.7±0.7	2.5±0.8	<0.01	2.7±0.8	2.2±0.6	0.01
Total cholesterol (mmol/L)	1448	11.1±2.0	11.6±2.2	10.8±2.3	<0.01	10.4±2.2	11.8±2.3	0.01
Triglycerides (mmol/L)	1448	5.5±3.2	7.2±3.7	9.9±7.7	<0.01	8.7±6.8	13.3±9.2	0.01

Data are means ±SD or n (%).
*P value for the three glycaemic statuses estimated with a Pearson's χ^2 test or a Fisher's exact test (categorical values) or with a Student's t-test (numerical values).
†P value for the two categories of diabetes awareness estimated with a Pearson's χ^2 test or a Fisher's exact test (categorical values) or with a Student's t-test (numerical values).
APA, aerobic physical activity; BMI, body mass index; EHES-LUX, European Health Examination Survey in Luxembourg; HDL, serum high-density lipoprotein cholesterol; hypertension, self-reported or measured hypertension; married, married or in a civil union; MSPA, muscle-strengthening physical activity; triglycerides, triglycerides concentration; WRPA, work-related physical activity.

South Korean studies (at least 20 but with no upper limit) could explain, at least in part, these discrepancies.

Factors associated with diabetes and prediabetes status

The high prevalence of prediabetes in Luxembourg is worrisome as this implies that numerous individuals may be at risk of developing diabetes in the near future. The present study provides novel evidence, which calls for urgent public health initiatives to raise the attention of policy makers in the country in order to tackle this neglected societal and economic burden. Indeed, there is currently no national screening programme for diabetes in Luxembourg, or for any other cardiometabolic condition, nor is there any public health initiative or programme to tackle the joint problems of diabetes and obesity in the country. Therefore, it is important to detect and monitor these high-risk factors.

We discuss here the major correlates of diabetes and prediabetes as observed in our study population. Findings on demographic factors associated with prediabetes and diabetes are fairly consistent with previous studies. In our study, prediabetes and diabetes concerned much more men than women but those differences were only significantly associated with prediabetes status. A statistically significant difference was also observed in Portugal with a higher diabetes prevalence observed in men compared with women.[29] Reasons for this remain poorly understood.[4] On the contrary, Kim *et al* in 2006[13] observed no association in Korea between prediabetes or diabetes and sex. Age was also a statistically significant factor associated with prediabetes and diabetes. This association was not observed among subjects with prediabetes in Kim *et al*'s study[13] but only in individuals with diabetes for which the statistically significant odds was 1.41 per 10 years. In our study, immigrant generation status was statistically associated with prediabetes and diabetes status. Being a second-generation immigrant was a protective factor for prediabetes status in comparison to a non-immigrant. Interestingly, Luxembourg is a country with a large cultural diversity where almost half of the people are foreign residents from more than 150 nationalities.[30] Migration phenomenon was and is still common in Luxembourg. The reasons for this association are unclear, but they might be linked to nutritional and lifestyle patterns, as well as to enhanced awareness and health-seeking behaviours among individuals who are expected to be better integrated in the Luxembourg context than their first-generation counterparts.[30] Family history of diabetes was also significantly associated with prediabetes and diabetes status. Even if the association was stronger for individuals with diabetes than for those with prediabetes, this population should not be neglected. Similar results were observed in Kim *et al*'s study[13] with also a strong association with diabetes and a statistically significant association with prediabetes. Abdominal obesity was statistically associated with individuals with prediabetes and diabetes, as already demonstrated by numerous studies.[11 13]

In our study, hypertension was significantly associated with diabetes but not with prediabetes status. Obviously, diabetes and high blood pressure share a number of potential risk factors (common soil hypothesis),[31] and are likely to cluster together along with other cardiometabolic abnormalities. The lack of a significant association between hypertension and prediabetes could be driven by a relatively healthier phenotype in individuals with prediabetes, which might protect them from the concomitant occurrence of high blood pressure,[32] but this needs to be supported by additional evidence. Regarding blood lipids, an increase in HDL cholesterol was significantly associated with a lower probability of prediabetes but not with diabetes status. Kim *et al*[13] in their study observed a

Table 3 Factors associated to different categories of diabetes status

	Diabetes (n=95) compared with no diabetes (n=1413)	Prediabetes (n=370) compared with normoglycaemia (n=986)
Age, years	1.05 (1.01, 1.09)	1.04 (1.02, 1.06)
Sex (Ref='Women')		
Men	1.51 (0.76, 2.97)	1.84 (1.30, 2.60)
Marital status (Ref='Not married or in a civil union')		
Married or in a civil union	NA	0.94 (0.69, 1.27)
Education (Ref='Primary')		
Secondary	0.99 (0.55, 1.80)	0.93 (0.65, 1.32)
Tertiary	1.03 (0.51, 2.09)	0.86
Immigrant origin (Ref='Not Immigrant')	NA	
First-generation immigrant		0.86 (0.63, 1.17)
Second-generation immigrant		0.61 (0.39, 0.95)
Fruits frequency (Ref='Less than once a day')	NA	
One or more a day		0.88 (0.66, 1.17)
Alcohol consumption (Ref= 'No drink')		
Two or three units per day or less	0.96 (0.52, 1.77)	1.38 (1.01, 1.89)
More than two or three units per day	1.58 (0.57, 4.33)	1.25 (0.65, 2.40)
Smoking (Ref= 'Never')	NA	
Current		1.37 (0.96, 1.96)
Ex-smokers		1.38 (0.98, 1.94)
Sleep in weekend (Ref= '<=6 hours')		
7–8 hours	0.8 (0.38, 1.65)	1.13 (0.75, 1.70)
>8 hours	0.97 (0.43, 2.15)	1.02 (0.64, 1.62)
WRPA (Ref= 'Mostly WRPA')		
No mostly WRPA	1.1 (0.60, 2.02)	0.88 (0.62, 1.24)
Not working	0.75 (0.37, 1.51)	0.87 (0.56, 1.34)
APA (Ref= '<150 min per week')		
≥150 min per week	1.11 (0.55, 2.25)	1.29 (0.94, 1.76)
MSPA (Ref= '<2 days per week')		
≥2 days per week	1.01 (0.43, 2.38)	1.18 (0.80, 1.72)
Diabetes family history (Ref= 'No')		
Yes	3.24 (1.95, 5.38)	1.52 (1.13, 2.05)
Abdominal obesity (Ref= 'No')		
Yes	2.63 (1.53, 4.52)	1.44 (1.06, 1.97)
Hypertension (Ref= 'No')		
Yes	3.18 (1.76, 5.72)	1.21 (0.88, 1.66)
Depression (Ref= 'No')		
Yes	1.88 (0.97, 3.64)	0.81 (0.56, 1.16)
Health perception (Ref= 'Good or very good')		NA
Fair, bad or very bad	1.39 (0.78, 2.46)	
Serum HDL cholesterol, mmol/L, one unit	1.29 (0.83, 2.01)	0.7 (0.54, 0.90)
Total cholesterol, mmol/L, one unit	0.74 (0.64, 0.86)	1.04 (0.96, 1.12)
Triglycerides concentration, mmol/L, one unit	1.16 (1.10, 1.22)	1.04 (0.99, 1.10)

Data are multivariable-adjusted OR (95% CI).
APA, aerobic physical activity; hypertension, self-reported or measured hypertension; MSPA, muscle-strengthening physical activity; NA, not selected in the multivariable logistic regression; WRPA, work-related physical activity.

protective association for this variable with both prediabetes and diabetes. Moreover, an increase in total cholesterol was statistically associated with a lower probability of diabetes but not with prediabetes. Hu *et al*[33] observed a significant positive association between total cholesterol and diabetes and also with prediabetes. In our study, higher triglycerides levels were significantly associated with a higher probability of diabetes but not with prediabetes. Kim *et al*[13] observed a deleterious association for this variable with diabetes (OR 1.23 per 1 mmol/L) but not with prediabetes.

Strengths and limitations

This study has several limitations. First, as in the majority of population-based studies around the world, a low participation rate was unfortunately observed. However, as explained in a previous study from the same survey,[19] the randomly selected sample initially contacted to participate in the survey (n=6396) and the actual respondents' sample (n=1451) did not differ according to age, sex and region, which should rule out the possibility of major selection bias. As a consequence, the study findings should be fairly applicable to the Luxembourg population, at least in the age range (25 to 64 years) of the EHES. Second, gestational diabetes was not investigated. This could generate a misclassification if female participants with history of gestational diabetes reported diabetes. However, this potential misclassification is likely to be marginal, as the general diabetes prevalence is not higher compared with neighbouring countries. Another limitation might be that glycaemic status was defined from FPG levels (compared with HbA1c levels) and not from Oral glucose tolerance test (OGTT) levels. However, as described in figure 1, there is a large overlap (almost 75%) between HbA1c and FPG criteria. Moreover, diagnosed and undiagnosed diabetes were differentiated and diagnosis of diabetes was determined from several sources (medication use, physician diagnosis and glycaemia measures) leading to an accurate estimation of diabetes prevalence. Finally, our study was restricted to 25–64-year-old adults, in line with the EHES protocol. Thus, the overall prevalence of prediabetes and diabetes would have been likely higher if older participants (≥65 years) had been recruited in the study, due to high life expectancy in Luxembourg as in other Western countries.

CONCLUSIONS

In our study, we observed that one in every three adults in Luxembourg may experience either prediabetes or diabetes in Luxembourg, supporting recent evidence showing that high blood glucose values are one of the top five risk factors for the overall burden of disease in the country.[34] We observed that risk factors such as age, family history of diabetes and abdominal obesity were common between diabetes and prediabetes. Thus, it is necessary to focus on prediabetes and diabetes high-risk population, with the support of national stakeholders, general practitioners and specialists, in terms of timely detection in primary care settings as well as health promotion and prevention campaigns in the community to limit diabetes-known complications of heart disease, retinopathy, neuropathy, kidney disease and depression. To measure the progress achieved to limit this burden, it would be relevant to conduct in the future other studies on diabetes in Luxembourg.

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REFERENCES

1. NCD Risk Factor Collaboration (NCD-RisC). Worldwide trends in diabetes since 1980: a pooled analysis of 751 population-based studies with 4.4 million participants. *Lancet* 2016;387:1513–30.
2. Beagley J, Guariguata L, Weil C, *et al*. Global estimates of undiagnosed diabetes in adults. *Diabetes Res Clin Pract* 2014;103:150–60.
3. Renard LM, Bocquet V, Vidal-Trecan G, *et al*. Adherence to international follow-up guidelines in type 2 diabetes: a longitudinal cohort study in Luxembourg. *PLoS One* 2013;8:e80162.
4. Tabák AG, Herder C, Rathmann W, *et al*. Prediabetes: a high-risk state for diabetes development. *Lancet* 2012;379:2279–90.
5. DECODE Study Group. Age- and sex-specific prevalences of diabetes and impaired glucose regulation in 13 European cohorts. *Diabetes Care* 2003;26:61–9.
6. Forouhi NG, Luan J, Hennings S, *et al*. Incidence of Type 2 diabetes in England and its association with baseline impaired fasting glucose: the Ely study 1990-2000. *Diabet Med* 2007;24:200–7.
7. Knowler WC, Fowler SE, Hamman RF, *et al*. 10-year follow-up of diabetes incidence and weight loss in the diabetes prevention program outcomes study. *Lancet* 2009;374:1677–86.
8. Stranges S, Rafalson LB, Dmochowski J, *et al*. Additional contribution of emerging risk factors to the prediction of the risk of type 2 diabetes: evidence from the Western New York Study. *Obesity* 2008;16:1370–6.
9. Qin X, Li J, Zhang Y, *et al*. Prevalence and associated factors of diabetes and impaired fasting glucose in Chinese hypertensive adults aged 45 to 75 years. *PLoS One* 2012;7:e42538.
10. Mainous AG, Tanner RJ, Baker R, *et al*Prevalence of prediabetes in England from 2003 to 2011: population-based, cross-sectional study. *BMJ Open* 2014;4:e005002.
11. Moody A, Cowley G, Ng Fat L, *et al*. Social inequalities in prevalence of diagnosed and undiagnosed diabetes and impaired glucose regulation in participants in the Health Surveys for England series. *BMJ Open* 2016;6:e010155.
12. Pierce MB, Zaninotto P, Steel N, *et al*. Undiagnosed diabetes-data from the English longitudinal study of ageing. *Diabet Med* 2009;26:679–85.
13. Kim SM, Lee JS, Lee J, *et al*. Prevalence of diabetes and impaired fasting glucose in Korea: Korean National Health and Nutrition Survey 2001. *Diabetes Care* 2006;29:226–31.
14. Bonaldi C, Vernay M, Roudier C, *et al*. A first national prevalence estimate of diagnosed and undiagnosed diabetes in France in 18- to 74-year-old individuals: the French Nutrition and Health Survey 2006/2007. *Diabet Med* 2011;28:583–9.
15. Alkerwi A, Sauvageot N, Donneau AF, *et al*. First nationwide survey on cardiovascular risk factors in grand-duchy of Luxembourg (ORISCAV-LUX). *BMC Public Health* 2010;10:468.
16. Perquin M, Michel GH, de Beaufort C, *et al*. Changes in diabetes prevalence and treatment in the last ten years in Luxembourg. A lesson from the United Kingdom prospective diabetes study? *Diabetes Metab* 2005;31:499–502.
17. Renard LM, Bocquet V, Vidal-Trecan G, *et al*. An algorithm to identify patients with treated type 2 diabetes using medico-administrative data. *BMC Med Inform Decis Mak* 2011;11:23.
18. Bocquet V, Barré J, Couffignal S, *et al*. Study design and characteristics of the Luxembourg European Health Examination Survey (EHES-LUX). *BMC Public Health* 2018;18:1169.
19. Ruiz-Castell M, Kandala NB, Kuemmerle A, *et al*. Hypertension burden in Luxembourg: Individual risk factors and geographic variations, 2013 to 2015 European Health Examination Survey. *Medicine* 2016;95:e4758.

20. Ruiz-Castell M, Kandala NB, Perquin M, *et al*. Depression burden in luxembourg: Individual risk factors, geographic variations and the role of migration, 2013-2015 European Health Examination Survey. *J Affect Disord* 2017;222:41–8.
21. Samouda H, Ruiz-Castell M, Karimi M, *et al*. Metabolically healthy and unhealthy weight statuses, health issues and related costs: Findings from the 2013-2015 European Health Examination Survey in Luxembourg. *Diabetes Metab* 2017.
22. American Diabetes Association. (2) Classification and diagnosis of diabetes. *Diabetes Care* 2015;38:S8–S16.
23. Department of Health. *Alcohol Guidelines Review–Report from the Guidelines development group to the UK Chief Medical Officers*. London: Department of Health, 2016.
24. Sharma M, Nazareth I, Petersen I. Trends in incidence, prevalence and prescribing in type 2 diabetes mellitus between 2000 and 2013 in primary care: a retrospective cohort study. *BMJ Open* 2016;6:e010210.
25. Unwin N, Shaw J, Zimmet P, *et al*. Impaired glucose tolerance and impaired fasting glycaemia: the current status on definition and intervention. *Diabet Med* 2002;19:708–23.
26. Heidemann C, Du Y, Schubert I, *et al*. [Prevalence and temporal trend of known diabetes mellitus: results of the German Health Interview and Examination Survey for Adults (DEGS1)]. *Bundesgesundheitsblatt Gesundheitsforschung Gesundheitsschutz* 2013;56:668–77.
27. Menke A, Casagrande S, Geiss L, *et al*. Prevalence of and trends in diabetes among adults in the United States, 1988-2012. *JAMA* 2015;314:1021–9.
28. Stöckl D, Rückert-Eheberg IM, Heier M, *et al*. Regional variability of lifestyle factors and hypertension with prediabetes and newly diagnosed type 2 diabetes mellitus: the population-based kora-f4 and ship-trend studies in Germany. *PLoS One* 2016;11:e0156736.
29. Gardete-Correia L, Boavida JM, Raposo JF, *et al*. First diabetes prevalence study in portugal: PREVADIAB study. *Diabet Med* 2010;27:879–81.
30. Alkerwi A, Sauvageot N, Pagny S, *et al*. Acculturation, immigration status and cardiovascular risk factors among Portuguese immigrants to Luxembourg: findings from ORISCAV-LUX study. *BMC Public Health* 2012;12:864.
31. Stranges S, Dorn JM, Donahue RP, *et al*. Oxidation, type 2 diabetes, and coronary heart disease: a complex interaction: findings from a population-based study. *Diabetes Care* 2008;31:1864–6.
32. Qiu M, Shen W, Song X, *et al*. Effects of prediabetes mellitus alone or plus hypertension on subsequent occurrence of cardiovascular disease and diabetes mellitus: longitudinal study. *Hypertension* 2015;65:525–30.
33. Hu Y, Teng W, Liu L, *et al*. Prevalence and risk factors of diabetes and diabetic retinopathy in Liaoning province, China: a population-based cross-sectional study. *PLoS One* 2015;10:e0121477.
34. Forouzanfar MH, Alexander L, Anderson HR, *et al*. Global, regional, and national comparative risk assessment of 79 behavioural, environmental and occupational, and metabolic risks or clusters of risks in 188 countries, 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013. *Lancet* 2015;386:2287–323.