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Prevalence of diabetes and impaired glucose metabolism in younger 'at risk' UK adults: insights from the STAND programme of research

EG Wilmot^{1,2}, CL Edwardson^{2,3}, SJH Biddle^{3,6}, T Gorely⁴, J Henson^{1,2,6}, K Khunti^{2,5,6}, MA Nimmo^{3,6}, T Yates^{2,5,6}, MJ Davies^{2,5,6}

1. Department of Cardiovascular Sciences, University of Leicester, University Hospitals of Leicester NHS Trust, Leicester General Hospital, Leicester, UK

2. Leicester Diabetes Centre, University Hospitals of Leicester, UK

3. School of Sport, Exercise and Health Sciences, Loughborough University, Loughborough, UK

4. School of Sport, Stirling University, Stirling, UK

5. Diabetes Research Unit, College of Medicine, Biological Sciences and Psychology, University of Leicester, UK

6. NIHR Leicester-Loughborough Diet, Lifestyle and Physical Activity Biomedical Research Unit

Corresponding Author and guarantor:

Dr Emma Wilmot

Leicester Diabetes Centre, Leicester General Hospital, Gwendolen Road
Leicester, UK LE5 4PW

Emma.Wilmot@uhl-tr.nhs.uk

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Novelty statements:

- NICE guidance (2012) recommends screening younger high risk individuals (aged 25-39 years) for diabetes.
- There is a lack of data on the prevalence of screen detected diabetes and impaired glucose metabolism in younger high risk UK adults.
- A cohort of younger high risk UK adults underwent an oral glucose tolerance test and HbA1c. 4.7% were diagnosed with Type 2 DM; 18.1% had impaired glucose metabolism.
- These findings lend support to the recent NICE recommendations but will require confirmation in larger studies.

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Abstract

Aims: Rising rates of obesity have led to an increasing prevalence of Type 2 diabetes mellitus (Type 2 DM) in young people. Uncertainty exists over the utility of screening younger adults for Type 2 DM as existing datasets have focused on mature (>40 years) cohorts. The aim of this study was to determine the prevalence of impaired glucose metabolism in higher risk younger adults.

Methods: Overweight (with an additional risk factor) or obese adults (18-40 years) were recruited for the Sedentary Time And Diabetes (STAND) randomised controlled trial. Measures included an oral glucose tolerance test (OGTT), HbA1c, biochemical and anthropometric data.

Results: 193 individuals (68% female; median age 33.8 years; median BMI 33.9 kg/m²) were recruited. 43% had a first degree family history of Type 2 DM. Previously undiagnosed Type 2 DM was present in 4.7% (n=9). 18.1% (n=35) had impaired glucose metabolism: 4.7% (n=9) HbA1c ≥48mmol/mol (6.5%); 9.3% (n=18) HbA1c 42-46mmol/mol (6.0-6.4%); 3.1% (n=6) Type 2 DM on OGTT; 6.2% (n=12) isolated impaired glucose tolerance (IGT); 2.1% (n=4) isolated impaired fasting glucose (IFG); 1% (n=2) both IFG and IGT. 58.5% (n=113) had dyslipidaemia, 28.0% (n=54) had hypertension, 31.1% (n=60) were vitamin D deficient and 7.3% (n=14) had abnormal liver function.

Conclusions: This study identified a high prevalence of Type 2 DM and impaired glucose regulation in overweight and obese younger adults. These findings require confirmation in a larger, representative, population.

Trial registration number: Current controlled trials ISRCTN08434554, MRC project 91409.

BACKGROUND

The appeal and availability of sedentary pursuits and energy dense foods, alongside lower levels of occupational and other physical activities, has culminated in a worldwide obesity epidemic across all age ranges. This change has driven a dramatic shift in the traditional profile of chronic disease, and we now increasingly witness the development of Type 2 DM in young people [1]. The diagnosis of Type 2 DM at a young age has profound implications for both the individual and society. It is asymptomatic in the initial stages resulting in many developing irreversible complications, often before therapy has even begun. At diagnosis, approximately half of younger adults with Type 2 DM have hyperlipidaemia and/or hypertension and one in five has microalbuminuria [2-4]. This accelerated development of micro and macrovascular complications has serious repercussions. For instance, those diagnosed <45 years of age have a 14-fold increase in the risk of myocardial infarction compared to those without diabetes; and a 4-fold increase in risk compared to age matched controls who had Type 2 DM diagnosed >45 years [5]. In addition, early onset Type 2 DM is associated with co-morbidities such as fatty liver disease and obesity, independent risk factors for mortality [6, 7]. Type 2 DM in the young is a relatively recent phenomenon with limited long term follow up data but it is likely that it will culminate in excess morbidity and mortality.

The early detection and management of Type 2 DM has the potential to reduce the impact of the disease. There is a legacy effect associated with early glycaemic control and even a modest delay in the diagnosis can have negative long term implications [8]. Identifying people at high risk of Type 2 DM presents an opportunity to intervene and prevent the development of Type 2 DM. There is now a wealth of evidence from studies of older adults which illustrate that progression to Type 2 DM can be prevented or delayed with lifestyle changes which include increased physical activity and dietary modification [9, 10].

The importance of the early detection of Type 2 DM in younger people has been acknowledged in the recent publication by the National Institute of Clinical Excellence (NICE) guidance which recommends screening high risk individuals aged 25-39 years of age [11]. Here, high risk includes black and minority ethnic groups (BME) and people with conditions that increase the risk of Type 2 DM. However, previous diabetes screening studies have predominantly focused on older adults, overlooking the potential disease burden in those younger than 40 years and the evidence base for this recommendation is currently lacking. We therefore investigated the prevalence of impaired glucose metabolism (IGM), Type 2 DM and cardiovascular risk factors in a multi-ethnic cohort of younger UK adults who were obese or overweight with at least one additional risk factor for the development of Type 2 DM.

METHODS

Study population and recruitment

In 2011, 193 young adults aged 18-40 years were recruited from across Leicestershire and Northamptonshire, UK as part of Project STAND, a 2-arm parallel group randomised controlled trial. The methodology for this trial has

been described in detail elsewhere [12]. The study was granted ethical approval by the local Research Ethics Committee. Informed verbal and written consent was obtained from all participants. Inclusion criteria were age 18-40 years with a BMI in the obese ($\geq 30\text{kg/m}^2$; $\geq 27.5\text{kg/m}^2$ for South Asians) or overweight range ($\geq 25\text{kg/m}^2$; $\geq 23\text{kg/m}^2$ for South Asians) plus an additional risk factor for Type 2 DM (family history of diabetes or cardiovascular disease in a first degree relative; previous gestational diabetes; polycystic ovarian syndrome). Exclusion criteria included significant illness, steroid use, pre-existing diabetes (self reported or recorded on GP database), pregnancy or an inability to communicate in English. Recruitment was co-ordinated via the East Midlands and South Yorkshire Primary Care Research Network. An electronic general practice (GP) database search was conducted to identify participants who met the inclusion criteria. Invitations were sent by the GP to the participants who then replied directly to the study team.

Study measures

Nurse administered questionnaires were used to assess medical history, drug and family history, smoking status and ethnicity. Arterial blood pressure was measured in the sitting position (Omron, Healthcare, Henfield, UK); three measurements were obtained and the average of the last two measurements used. Hypertension was defined as a systolic blood pressure ≥ 140 or diastolic ≥ 90 mmHg or treatment for hypertension [13]. Other measures included body weight and body fat percentage (Tanita BC 420SMA, Tanita, West Drayton, UK), waist circumference (midpoint between the lower costal margin and iliac crest), and height to the nearest 0.1 kg, 0.5% and 0.5 cm respectively.

Glycaemia

Participants were invited to attend a baseline measurement session after a 12-hour fast and 24 hours of avoiding vigorous intensity exercise. Individuals underwent a standardized 75g OGTT and an HbA1c to measure glycaemia. HbA1c was interpreted according to the 2011 WHO criteria (HbA1c $\geq 48\text{mmol/mol}$ (6.5%) diabetes; 42-46 mmol/mol (6.0-6.4%) "high risk") [14, 15]. The OGTT results were interpreted according to the 1999 WHO criteria and divided into diabetes, isolated impaired fasting glycaemia (IFG), isolated impaired glucose tolerance (IGT) or impaired glucose regulation (IGR) (both IFG and IGT) [16]. In this study, diabetes is defined by an OGTT and/or HbA1c result in the diabetes range. Impaired glucose metabolism (IGM) refers to any previously undiagnosed glucose abnormality including an HbA1c $\geq 42\text{mmol/mol}$ (6%) and/or OGTT defined IFG, IGT or Type 2 DM.

Laboratory analysis

Serum total cholesterol, HDL cholesterol, and triglycerides; liver function, urea and creatinine and 25-hydroxyvitamin D were measured. Low density lipoprotein cholesterol (LDL) was estimated using the Friedewald equation [17]. Dyslipidaemia was defined as lipid lowering treatment or triglycerides ≥ 1.7 mmol/l or HDL < 1.03 (males) and < 1.29 mmol/l (females) [18]. Plasma glucose, lipids and liver function tests were all measured using standard enzymatic endpoint methods on an ADVIA Chemistry System (Bayer Healthcare, NY, USA). An abnormal ALT was defined as $> 53\text{iU/L}$. HbA1c was measured by ion exchange liquid chromatography (G7; Tosoh, Tokyo, Japan).

25-Hydroxyvitamin D (25(OH)D) was quantified using liquid chromatography mass spectrometry (6410 Triple Quad, Agilent Technologies UK Ltd, Wokingham, UK).

Statistical methods

Normality was assessed using the Kolmogorov-Smirnov test, histograms and normal Q-Q plot. Continuous data were expressed as mean (standard deviation (SD)) if they were normally distributed. Non-parametric continuous variables were expressed as median (25% and 75% interquartile range (IQR)). Categorical data were expressed as a percentage. Chi square was used to compare categorical variables between two groups. Statistical tests were performed using SPSS 18.0 software (Statistical Package for the Social Sciences, Chicago, IL). $p < 0.05$ was considered statistically significant.

RESULTS

193 participants who completed the STAND study baseline visit were included. 68% (n=131) were female. 21% (n=40) were of BME origin (Asian n=23; Black n=10; mixed ethnic origin n=7). Median (+/-interquartile range) age and BMI were 33.8 (29.3-37.9) years and 33.9 (31.2-37.6) kg/m² respectively. 43% had a first degree family history of Type 2 DM. Baseline anthropometric and laboratory data are described in Table 1.

Prevalence of impaired glucose metabolism

Diabetes was present in 4.7% (n=9) of the study population. IGM was present in 18.1% (n=35). Of those with IGM, 4.7% (n=9) had an HbA1c ≥ 48 mmol/mol (6.5%); 9.3% (n=18) HbA1c 42-46mmol/mol (6.0-6.4%); 3.1% (n=6) Type 2 DM on OGTT; 6.2% (n=12) isolated IGT; 2.1% (n=4) isolated IFG; 1% (n=2) both IFG and IGT. 32.5% (n=13) of the BME population had IGM compared to 14.5% (n=22) of the White Caucasian population ($p=0.01$). 15.3% (n=20) of females had IGM compared to 24.2% (n=15) males ($p=0.13$). All participants aged <25 years (n=22) had normal glucose status.

Cardiometabolic risk

58.5% (n=113) had dyslipidaemia and 28.0% (n=54) had hypertension. 0.5% (n=1) and 4.7% (n=9) were prescribed lipid lowering and anti-hypertensive therapy respectively. 7.3% (n=14) had an elevated alanine transferase, a marker of possible fatty liver disease. 31.1% (n=60) were vitamin D deficient (<30nmol/l).

CONCLUSIONS

Screening young overweight and obese adults for Type 2 DM successfully identified diabetes (4.7%) and impaired glucose metabolism (18.1%). The diabetes yield in this cohort was similar to other larger screening studies in older UK populations and adds further support to the recent national recommendation to screen those aged 25-39 years for diabetes [11].

The ADDITION-Leicester population based diabetes screening study, with a mean age 57 years, identified 3.3% of the population with undiagnosed Type 2 DM [19]. These data were based on OGTT results and are comparable with

the OGTT diabetes yield (3.1%) in the younger high risk STAND cohort. Similar figures have been reported in other UK studies in overweight and obese populations >40 years, with reported yields between 1.4% and 5.4% [20, 21]. However, it is important to highlight that the STAND cohort were a high risk group and not representative of the general Leicester population. In Leicester 23% of the population are obese and 36% of BME origin compared to 89% and 21% of the STAND study population respectively [22,23]. The BME populations were underrepresented in this study, a group which typically has more than double the prevalence of screen detected diabetes [19]. These factors limit the generalisability of our findings. Nonetheless, the yield obtained highlights that undetected Type 2 DM is prevalent in high risk young cohorts and is worth pursuing. Furthermore, NICE recommend targeted screening towards minority ethnic groups, a recommendation supported by our finding of significantly more IGM in the BME group. However, the prevalence of IGM (14.5%) and Type 2 DM (2%) in the White Caucasian population was still considerable. The increasing prevalence of abnormal glucose metabolism in younger White Caucasian adults is recognised and requires further exploration in larger studies [24].

The prevalence of IGM in this younger population has implications for clinical practice. Type 2 DM in younger people represents an aggressive phenotype with multiple co-morbidities (hyperlipidaemia, non alcoholic fatty liver disease, morbid obesity) and the rapid development of complications such as nephropathy and hypertension, often more quickly than people with Type 1 DM and despite relatively tight glycaemic control [2]. Early detection of Type 2 DM in this group is paramount in order to prevent the development of irreversible complications during their working lives. This is particularly important in young women of child bearing age. If a woman with undiagnosed Type 2 DM becomes pregnant, there is substantial risk to the unborn foetus, particularly during organogenesis in the first trimester when congenital defects occur in the presence of uncontrolled hyperglycaemia [25]. Such risks can be minimised by tight glycaemic control and high dose folic acid in early pregnancy [25]. In view of the high rates of IGM in our young cohort, it would seem sensible to consider diabetes screening in obese women and overweight women with a family history of diabetes or cardiovascular disease. The main strengths of this study are the unique insights into the prevalence of dysglycaemia and cardiovascular risk factors in a younger high risk UK population. However, interpretation of the data requires some caution given the sample size, small in comparison to large diabetes screening studies. Also, these participants were motivated subjects who volunteered for inclusion in a randomised controlled behavioural intervention trial on the basis of being 'at risk', and this may limit how generalisable the findings are. However, few data are available on the prevalence of impaired glucose metabolism in this group so the findings of this study fill a gap in current knowledge.

In conclusion, screening for Type 2 DM in a high risk multi-ethnic population of younger adults successfully identifies Type 2 DM and IGM. The findings will need confirmation in larger populations.

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Competing interests

The authors declare that they have no competing interests.

Authors contributions

The original study proposal ideas were led by SJHB, MD, TG, KK, MN, and TY. EW and CE participated in the design, management and coordination of the study. EW, CE, TY and JH collected and analysed data. EW wrote the first draft of the manuscript. All have been involved in revising the content of the manuscript. All authors have read and approved the final manuscript.

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Table 1. Anthropometric and laboratory outcomes

Descriptive (n=187-193)	n=	Median/% (IQR)	95% CI
Age (years)	193	33.8 (29.3-37.9)	32.1-33.7
Gender (% female)	193	67.9	
Ethnicity (% BME)	193	20.7	
Systolic BP (mmHg)	193	119 (112-129)	119.1-123.2
Diastolic BP (mmHg)	193	83 (78-89)	82.7-85.5
BMI (kg/m ²)	193	33.9 (31.2-37.6)	33.9-35.3
Obese (%)	193	88.6	
Waist (cm)	193	101 (94-111)	102-105
Waist Hip Ratio	193	0.88 (0.81-0.95)	0.87-0.90
Body fat (%)	193	41.9 (35.2-46.2)	39.6-41.6
Fat free mass (%)	193	53.9 (49.4-66.3)	55.7-59.4
Cholesterol (mmol/l)	192	4.8 (4.2-4.8)	4.8-5.1
LDL (mmol/l)	188	3.0 (2.4-3.4)	2.9-3.1
HDL(mmol/l)	191	1.2 (1.0-1.4)	1.2-1.3
Trig(mmol/l)	192	1.3 (0.9-1.9)	1.4-1.8
HbA1c (mmol/mol)	191	46 (36-40)	38-39
HbA1c (%)	191	5.6 (5.4-5.8)	5.6-5.7
Fasting glucose (mmol/l)	192	4.8 (4.5-5.1)	4.8-5.2
2 hour glucose (mmol/l)	192	5.2 (4.3-6.4)	5.3-6.1
ALT (iu/l)	192	23 (17.34)	26.0-31.2
AST (iu/l)	187	22 (18-29)	23.2-25.7
Vitamin D <30nmol/l (%)	190	31.1	

Results presented as median (interquartile range (IQR)) or percentage (%). BME = black or minority ethnic group.