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ORIGINAL RESEARCH

Is the Current Cut Point for Glycated Haemoglobin (HbA1c) Correct for Diagnosing Diabetes Mellitus in Premenopausal Women? Evidence to Inform Discussion

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ABSTRACT

Introduction: Women are on average diagnosed with diabetes mellitus at later age than men but have higher mortality. As the diagnosis of diabetes mellitus is primarily based on HbA1c, the use of a non-specific reference range and cut point for diabetes mellitus that does not account for gender differences in diabetes could potentially lead to underdiagnosis of diabetes mellitus in women and missed opportunities for intervention. We investigated whether a contributing factor to the later diagnosis in women may be a difference in distribution of HbA1c in premenopausal women versus men of the same age by comparing HbA1c values in men and women across multiple sites in the UK.

Methods: We analysed the HbA1c levels of 146,907 individuals who underwent single

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testing only and had HbA1c ≤ 50 mmol/mol between 2012 and 2019 in one laboratory (cohort 1). This was replicated in six laboratories with 938,678 individuals tested between 2019 and 2021 (cohort 2).

Results: In cohort 1, women < 50 years old had an HbA1c distribution markedly lower than that in men by a mean of 1.6 mmol/mol ($p < 0.0001$), while the difference in the distribution of HbA1c for individuals aged ≥ 50 years was less pronounced (mean difference 0.9 mmol/mol, $p < 0.0001$). For individuals under the age of 50, HbA1c in women lagged by up to 10 years compared to men. Similar findings were found in cohort 2.We estimated an additional 17% ($n = 34,953$) of undiagnosed women aged < 50 years in England and Wales could be reclassified to have diabetes mellitus, which may contribute to up to 64% of the difference in mortality rates between men/women with diabetes mellitus aged 16–50 years.

Conclusion: The HbA1c cut point for diagnosis of diabetes mellitus may need to be re-evaluated in women under the age of 50 years. Early identification of diabetes mellitus in women has the potential to improve women's health outcomes in the longer term.

Keywords: Diabetes mellitus; Sex difference; Haemoglobin A1c; Diagnostic controversies; Epidemiology

Key Summary Points

In our analysis of over one million individuals in England, we showed that women < 50 years old had an HbA1c distribution that was markedly lower than that in men by a mean of 1.6 mmol/mol.

The HbA1c in these women lagged by up to 10 years compared to men under the age of 50.

We estimated an additional 17% of undiagnosed women aged < 50 years could be reclassified to have diabetes mellitus.

Our findings provide evidence that the HbA1c cut point for diagnosis of diabetes mellitus may need to be re-evaluated in women under the age of 50.

INTRODUCTION

Diabetes is a major public health issue that causes premature mortality both directly and through its associated complications [1]. Globally, approximately 537 million adults are living with diabetes [2], with 86% being affected by type 2 diabetes mellitus (T2D) [3]. There are known sex and gender differences in diabetes

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mellitus and diabetes-mediated risk of cardiovascular disease [4, 5]. For example, the age of diagnosis of diabetes mellitus is higher in women than in men [6]. Although non-diabetic hyperglycaemia (NDH; previously commonly referred to as pre-diabetes) is more often observed in women, fewer women are being diagnosed with diabetes mellitus compared with men [7]. NDH is known to be associated with higher all-cause mortality in men and women [8]. However, the risk of composite cardiovascular disease is higher in women with NDH than men with NDH [8]. At the time of diabetes mellitus diagnosis, women have a higher risk factor burden such as obesity [9] and hypertension [10]. In addition, women with diabetes mellitus have worse health outcomes as manifested by poorer glycaemic control [11], higher risk of cardiovascular complications [12] and death [13], as well as higher standardised mortality ratio (SMR) [14], compared with men.

Glycated haemoglobin (HbA1c) is increasingly becoming the accepted diabetes mellitus screening test globally, supplanting the previous approaches of fasting glucose measurement or oral glucose tolerance test. However, there remains debate about the use of HbA1c as a diagnostic tool [15]. As an index of long-term blood glycaemic control and a risk predictor, the HbA1c measure has become an indispensable part of routine management of diabetes since the 1980s. HbA1c test results are standardized to the International Federation of Clinical Chemistry (IFCC) Reference Measurement Procedure (RMP) [16] in harmony with the National Glycohemoglobin Standardization Program (NGSP) [17]. Glycated haemoglobin is dependent on the individual's erythrocyte cell lifespan [18], which can vary between different individuals [19] and age groups [20]. For example, HbA1c underestimates average glucose levels in conditions that shorten the average erythrocyte lifespan, including iron deficiency anaemia, haemolysis, and sickle cell disease [18].

Glycated haemoglobin is considered as an overall measure of average blood glucose levels over the previous 120 days [21]. However, the reference range for HbA1c was based on a small study conducted on 205 individuals with type 1 diabetes and 124 controls without diabetes [22], without reporting of the number of male and female study participants.

In premenopausal women, the HbA1c has been reported as lower than men of the same age [23, 24]. This may be due to menstruation and hence shorter erythrocyte survival which results in shorter exposure of haemoglobin to glucose compared with individuals who do not menstruate. Given that the diagnosis of diabetes mellitus is also based on HbA1c, the use of a non-specific reference range and cut point for diabetes mellitus for premenopausal women could potentially lead to underdiagnosis of diabetes mellitus in women and missed opportunities for intervention. Therefore, we investigated whether there is a difference in distribution of HbA1c in premenopausal women versus men of the same age by comparing HbA1c values in men and women across multiple sites in the UK. We also estimated the number of women who could be diagnosed with diabetes mellitus using this new reference range.

METHODS

Using Laboratory Information and Management Systems, we extracted data on all HbA1c requests received between 1 January 2012 and 31 December 2019 from the University Hospitals of North Midlands NHS Trust (UHNM) Clinical Biochemistry Department (cohort 1). In parallel, data on all HbA1c test requests between 1 January 2019 and 31 December 2021 were extracted from six other Clinical Biochemistry Departments (cohort 2): Cambridge University Hospitals NHS Foundation Trust (CUH); Countess of Chester Hospital NHS Foundation Trust (COCH); Pennine Acute Hospitals NHS Trust (PAH); Salford Royal NHS Foundation Trust (SRFT); St Helens and Knowsley Teaching Hospitals NHS Trust (STHK); and Warrington & Halton Hospitals NHS Trust (WHH). These two cohorts over seven sites serve an estimated population of 4,383,288. Assuming an UK population of 67,026,292 (2021 figure [25]), this equates to 6.5% of the UK population. Data on the areas covered by the laboratories were

obtained from National Health Service Digital [25], based on the GP practices served by each laboratory. We selected these seven sites to include a wide range of population demographics.

We extracted data on the following standardised set of parameters: unique patient ID (anonymised), test result, date of request, age, and sex. We included individuals who only had a single HbA1c test during the study periods as these individuals are likely to be healthy and without an established diagnosis of diabetes. Standard laboratory procedures were used to measure HbA1c. For all laboratories, the assay was within the scope of the laboratory's ISO 15189 accreditation, as overseen by the United Kingdom Accreditation Service [26]. Throughout the study period, the assay demonstrated acceptable performance on routine Internal Quality Control and External Quality Assurance parameter across all seven sites. We obtained permission from the relevant laboratory leads at each of the seven sites to access and use the data from their Laboratory Information and Management Systems. The study was in accordance with the Declaration of Helsinki. This study is part of an audit and quality improvement programme to increase the quality of laboratory test requesting. Hence, it includes a service evaluation and audit of local practice against the guidelines outlined by the National Institute for Health and Care Excellence (NICE) [27, 28] with a view to increasing implementing quality improvements to enhance the clinical laboratory service. Accordingly, this study was not considered to be research using the decision tool provided by the UK Health Research Authority [29] and did not require NHS Research Ethics Committee review. All data were fully anonymised prior to transfer for analysis.

Effect size on mortality was estimated by extrapolating findings based on the Office of National Statistics population data [27, 28] and the National Diabetes Audit published diabetes mellitus prevalence and related excess mortality [29] in England and Wales. All statistical analyses were performed using Stata/MP version 17.0 (College Station, Texas). We expressed the overall HbA1c values in men and women in the two age groups (< 50 vs ≥ 50 years) as means ± standard deviations (SD), while those in individual age groups were expressed as median values because of the non-normal distributions in some age groups where numbers were smaller. Differences between groups were analysed using Student's t tests. Statistical significance was set at $p < 0.05$. There was no patient and public involvement in this service evaluation project.

RESULTS

Impact of Age and Sex on HbA1c Levels

We examined healthy individuals who had one HbA1c test with HbA1c between 20 and 50 mmol/mol at UHNM (cohort 1, n = 146,907, Table 1). We plotted the relative frequency of various HbA1c values in women and men above and below the age of 50 (Fig. 1a). The plot in Fig. 1a takes HbA1c up to 50 mmol/mol in order to reduce the likelihood of possible artefacts due to HbA1c test coefficient of variation (CV), by broadening the HbA1c limits. We showed that there was a 1.6 mmol/mol difference ($p < 0.0001$) between women (mean ± SD 34.4 ± 5.7) and men (mean ± SD 36.0 ± 7.5) for those aged below 50. For individuals aged ≥ 50 years, the difference was also present ($p < 0.0001$), yet less marked ($p < 0.0001$) between women (mean ± SD 39.1 ± 8.0) and men (mean ± SD 40.0 ± 9.9). On the basis of current epidemiology [30], we defined premenopausal women as under 50 years of age, as we did not have access to individual patient level data concerning fertility status.

We also calculated at each HbA1c value the ratios for women versus men as the ratio of proportion of women to proportion of men with each HbA1c value within cohort 1 (Supplemental Table 1). For example, at HbA1c of 48 mmol/mol, 50% fewer women (ratio 0.5) could be diagnosed with diabetes mellitus than men under the age of 50, whilst only 20% fewer women (ratio 0.8) could be diagnosed with diabetes mellitus than men over or equal to the age of 50.

We next assessed the trend in median HbA1c with age at the time of testing, stratified by sex (Fig. 2a). This demonstrated the expected rise in HbA1c with increasing age. It also showed that there was a sex difference between women (after the usual age of the menarche) and men under the age of 50, with the HbA1c lagging by up to 10 years in women compared to men. For example, a median HbA1c of 36 was observed in men as young as 34–36 years of age and in women as young as 46–47 years of age (Fig. 2a). Taken together, an undermeasurement of approximately 1.6 mmol/mol HbA1c in women may delay their diabetes mellitus diagnosis by up to 10 years.

To validate our results, we replicated the previous analyses on HbA1c and age in a large cohort from six other NHS Trusts (cohort 2, $n = 938,678$) during the period 2019–2021 (Table 1, Figs. 1b, 2b, Supplemental Table 2). The plot in Fig. 1b takes HbA1c up to 50 mmol/mol in order to reduce the likelihood of possible artefacts due to HbA1c CV, by broadening the HbA1c limits. Similar findings were demonstrated. Data from the individual trusts (CUH, COCH, PAH, SRFT, STHK, WHH) are shown in Supplemental Fig. 1.

Implications of Lowering Threshold for Diabetes Mellitus Diagnosis

As we showed that in individuals aged < 50 years, HbA1c level is, on average, 1.6 mmol/mol lower in women than men (Fig. 1), we wished to quantify the potential effects of lowering the threshold for diagnosis of diabetes mellitus from HbA1c of 48 to 46 mmol/mol for women under the age of 50. This study examined the HbA1c levels of 146,907 individuals (cohort 1) who only had one HbA1c test and therefore could be considered to not have been diagnosed with diabetes. Of the individuals tested, 75,331 were women aged ≥ 16 years with a HbA1c of 48 mmol/mol or less. Of these women, 43,253 were aged 16–50 years. Within this group of women, there were 113 women who had an HbA1c value of 46 or 47 mmol/mol, i.e. 0.26% of this group could have been diagnosed as having diabetes mellitus if the HbA1c cut point for diabetes mellitus diagnosis was lowered to 46 mmol/mol for women aged 16–50 years.

To put this percentage into a population context, the UK Office for National Statistics estimated that there were 13,652,443 women aged between 16 and 50 years in England and Wales in 2021 [25]. By deducting 208,090 women known to have diabetes aged between 16 and 50 years from the National Diabetes Audit 2021–2022 in England and Wales [31], we estimate there are 13,443,353 women who have not been diagnosed with diabetes in this age group. Extrapolating our finding that 0.26% of this age group could have diabetes mellitus using a lower HbA1c cut point, 34,953

Table 1 Characteristics of the study cohort

	Cohort 1	Cohort 2					
	UHNM	CUH	COCH	PAH	SRFT	STHK	WHH
Individuals tested	146,907	268,996	58,835	207,463	182,269	150,393	70,723
Median age of all individuals (years)	48	52	43	44	50	51	50
Proportion of women tested	54.5%	57.1%	57.1%	56.4%	54.8%	57.7%	56.9%
Total population covered	667,884	1,210,428	247,048	869,694	500,381	611,449	276,404

CUH Cambridge University Hospitals NHS Foundation Trust, *COCH* Countess of Chester Hospital NHS Foundation Trust, *PAH* Pennine Acute Hospitals NHS Trust, *SRFT* Salford Royal NHS Foundation Trust, *STHK* St Helens and Knowsley Teaching Hospitals NHS Trust, *UHNM* University Hospitals of North Midlands NHS Trust, *WHH* Warrington & Halton Hospitals NHS Trust

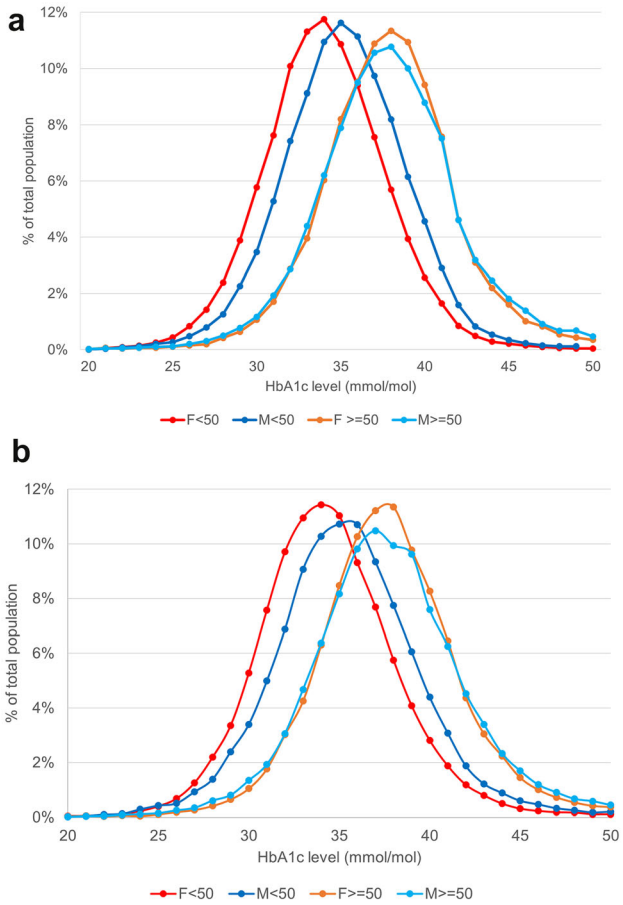

Fig. 1 Distribution of HbA1c by sex and stratified by age < 50 and ≥ 50. **a** Cohort 1, **b** cohort 2

additional women could be diagnosed with diabetes mellitus in England and Wales.

The National Diabetes Audit recorded 1,425,495 women with diabetes, with 208,090 of these aged 16–50 years [31]. By including 34,953 additional women with diabetes mellitus aged 16–50 years using the lower HbA1c cut point, the percentage of younger women with diabetes would increase by 17% in England and Wales. How this diagnosis at younger age would then impact on the total prevalence at older age was not quantified.

DISCUSSION

In our analysis of over one million individuals having single HbA1c tests at seven NHS Trusts across England, we showed there is a sex difference in median HbA1c relative to age in individuals younger than 50 years old, with HbA1c lagging by up to 10 years in women. We also showed that women have lower HbA1c by 1.6 mmol/mol than men of the same age. Furthermore, if the threshold for diagnosis of diabetes mellitus was lowered by 2 mmol/mol in women under the age of 50, an additional 17% of these women (approximately equivalent to 35,000 women in England and Wales) would be diagnosed with diabetes mellitus.

Given the broad-based sampling frame, our findings have wide applicability across populations, such as in North America and Europe. We speculate that the HbA1c testing could have been done in individuals at high risk of developing diabetes mellitus. However, as we included only individuals who had one HbA1c test, these individuals are unlikely to have been diagnosed with diabetes mellitus as such people

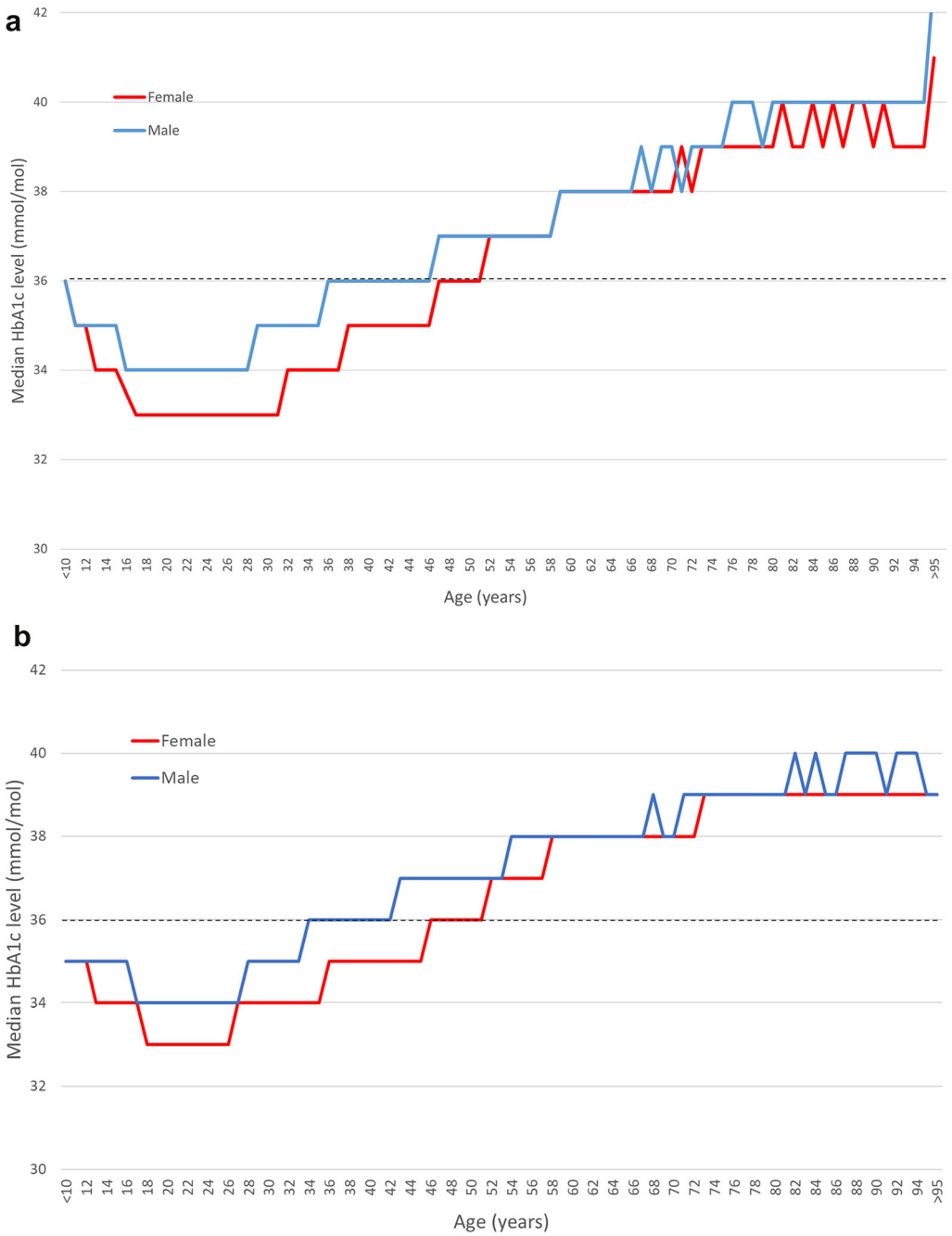

Fig. 2 Median HbA1c level throughout the age range, stratified by sex. **a** Cohort 1, **b** cohort 2

require regular HbA1c testing to monitor their diabetes control.

In keeping with previous literature, we found an increase in HbA1c with age in non-diabetic men and women [32]. In addition, previous studies have looked at the matter of sex differences in HbA1c in relation to menopause. The distribution of HbA1c was reported to be approximately Gaussian, with a slight difference between mean and median values at all ages in both sexes whilst HbA1c levels rose after the age of 50 in women [33]. However, the

implication of differing HbA1c reference ranges on delayed diabetes mellitus diagnosis with worsening cardiovascular risk profile has not been previously recognised. We highlight for the first time that, while 1.6 mmol/mol may appear only a small difference in terms of laboratory measurement, at a population level this has implications for significant number of premenopausal women.

We showed that HbA1c levels in women aged < 50 years were consistently lower than in men and that women reach the equivalent levels to those in men up to 10 years later, which may result in delayed diagnosis of diabetes mellitus in premenopausal women. We also found a less marked gender difference for individuals aged ≥ 50. However, this was outside the scope of the present paper and warrants further targeted research, while having potential implications for the development of diabetes-related complications in women. The later diagnosis in women does not appear to be the result of less frequent testing in premenopausal women. Indeed, our data on the number of tests in our cohorts suggest that women are tested more frequently than men (Table 1, Supplemental Table 2).

As normal erythrocyte survival is approximately 120 days [34], if women lose approximately 50 ml out of 5 L blood in circulation during each menstrual cycle [35], this is equivalent to 200 ml over four menstrual cycles or 4% of overall circulating blood. This 4% approximately equates to 1.9 mmol/mol in those with a HbA1c value of 48 mmol/mol in women under 50 years of age which is in line with the difference in HbA1c we observed between men and women aged < 50 years.

Sex and gender differences in adverse cardiovascular risk factors are known to be present prior to the development of diabetes mellitus [36]. Once diagnosed, the prevalence of atherosclerotic cardiovascular disease is twice as high in patients with diabetes mellitus compared to those without diabetes mellitus. For women, diabetes mellitus is a stronger risk factor for cardiovascular disease than for men [13, 37, 38]. Women with diabetes aged 35–-59 years have the highest relative cardiovascular death risk across all age and sex groups [13]. Furthermore, there is disparity in cardiovascular risk factor management between men and women [39], including in high-risk groups such as women with diabetes mellitus [40, 41]. Women are less likely than men to receive treatment and cardiovascular risk reduction care that are recommended by international guidelines on diabetes [42]. In addition, compliance to medication or prescription treating cardiovascular risk factors is lower in women than men with diabetes mellitus, with less use of statins, aspirin and beta blockers [43]. Timely diagnosis of diabetes mellitus and initiation of preventative treatment has the potential to improve cardiovascular risk profile over lifetime and facilitate a longer life expectancy in women.

In terms of mortality, diabetes mellitus is associated with a reduced life expectancy with women being particularly affected (5.3 years shorter vs 4.5 years for men) [44]. Data from the National Diabetes Audit indicate that the relative mortality rate ratio for people with diabetes mellitus aged 16–50 years, compared to the general population, is 26.7% higher in women than men of the same age (2.56 for women versus 2.02 for men) [31]. Although the additional women (approx. 35,000) diagnosed with diabetes mellitus using our proposed lower HbA1c cut-off are unlikely to contribute to excess mortality, these additional cases would add to the denominator in the calculation of mortality rates in women. This sex difference was recently highlighted in a population-based study [44] which reported that 55% of excess diabetes mellitus female deaths were attributed to sex difference in the prevalence of adverse and protective factors.

Strengths and Limitations

Some limitations of our study come from the utilization of laboratory data lacking specific information, such as the reason for HbA1c testing, age of menopause in the women whose HbA1c was measured, fasting plasma glucose levels, prescription of oestrogen-containing contraceptive preparations or hormone replacement, and menstrual cycle length,

frequency, duration, and amount of blood loss. We also do not know why the screening HbA1c test was arranged. More HbA1c tests were done in women which may relate to opportunistic screening picking up more healthy women than men in the course of routine general practice attendance around women's health matters in comparison with men aged 40–60 years who are less likely to attend for routine health checks than are women.

Also, taking 50 years of age as a threshold for menopause is only a rough approximation in the absence of clinical data. Nevertheless, the vast number of HbA1c tests across several laboratories showed that there is an age point of around 50 years at which the difference between men and women and the HbA1c distribution decreases drastically, and this somehow reinforces the approximation mentioned above.

Another limitation is that we only had one test per person and took it as an indirect sign of a non-diabetic condition. Such an interpretation could be doubted in cohort 2, which pertained to the COVID-19 pandemic period when there may have been a reduction in the overall number of HbA1c tests performed [44]. However, the strengths of our study, i.e. the large number of individuals tested and the fact that similar findings were reproduced across multiple hospital sites, make possible doubts about that less credible.

As a part of the study period for cohort 2 occurred during the COVID-19 pandemic, there may have been a reduction in the overall number of HbA1c tests performed during this time [45].

A strength of our study is the large number of individuals tested and that similar findings were reproduced across multiple hospital sites.

CONCLUSION

We suggest that the threshold for diagnosis of diabetes mellitus may be too high by approximately 2 mmol/mol in women under the age of 50, which may result in 17% of all premenopausal women missing their diabetes mellitus diagnosis. We estimated that for England and Wales, moving the threshold for diagnosis of diabetes mellitus to 46 mmol/mol from 48 mmol/mol would reclassify approximately 35,000 women as having diabetes mellitus. More work is ongoing to explore the long-term implications of our findings. Further research is needed regarding the most effective implementation strategy to change the diagnostic cut-off.

We acknowledge that the logistics of changing the diagnostic cut-off for HbA1c in this group of women may be challenging. One alternative approach may be to offer further assessment using fasting plasma glucose or oral glucose tolerance testing in those with HbA1c values of 46 or 47 mmol/mol. We accept that any such categorisation based on HbA1c is always an approximation but if the targeting of therapy to optimise cardiovascular risk factor profile improves life quality and expectancy, such a reclassification will prove to have been worthwhile.

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which was then critiqued by all other authors as part of regular team meetings and the manuscript revision process. All authors approved the final version of the manuscript. Pensee Wu is guarantor.

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Data Availability. The data that supports the findings of the study are not publicly available due to privacy restrictions. However, extracts of data will be made available to researchers on reasonable request. Adrian Heald is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Declarations

Conflict of Interest. All authors declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

Ethical Approval. The study was in accordance with the Declaration of Helsinki. This study is part of an audit and quality improvement programme to increase the quality of laboratory test requesting. Hence, it includes a service evaluation and audit of local practice against the guidelines outlined by NICE with a view to increasing implementing quality improvements to enhance the clinical laboratory service. Accordingly, this study was not considered to be research using the decision tool provided by the UK Health Research Authority and did not require NHS Research Ethics Committee review.

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