



The Impact of Age and Sex on Fasting Plasma Glucose and Glycated Haemoglobin (HbA1c) in the Non-diabetes Population

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ABSTRACT

Introduction: We previously reported sex differences in the distribution of glycated haemoglobin (HbA1c) for men/women aged < 50 years vs older individuals, with implications for delayed diabetes diagnosis. Here, we explored whether this pattern was also seen in matched fasting plasma glucose (FPG) levels.

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Methods: We extracted data on same-day, paired HbA1c and FPG levels from clinical biochemistry laboratory databases from Mersey and West Lancashire Teaching Hospitals NHS Trust ($n=10,153$) and Cambridge University Hospitals NHS Foundation Trust ($n=10,022$) between Jan 2019 and Dec 2023. Only cases with a single, general-practice HbA1c test were utilised to minimise the risk of including non-diagnostic tests and tests from specialist care (e.g. endocrinology, antenatal services; final dataset: $n=17,271$). We examined the links of HbA1c and FPG levels to age and sex.

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Results: Median HbA1c levels were 1 mmol/mol lower in women aged <45 years compared to men aged <45 years but not in those aged ≥45 years. This pattern was *not* seen with FPG, where median levels in women were 0.1–0.2 mmol/L lower across all ages. The HbA1c:FPG ratio was significantly higher in women than men in the 45–54 and ≥55 years age groups ($p=0.004$, $Z\text{-score}=2.9$ and $p<0.001$, $Z\text{-score}=8.9$, respectively) but not in the <45 years age group ($p=0.649$, $Z\text{-score}=0.5$). We confirmed our previous finding that median HbA1c levels in women aged ≥55 years and 45–55 years were the same as those in men (39 and 37 mmol/mol, respectively) and that for women aged <45 years, the median HbA1c (34 mmol/mol) was 1 mol/mol lower than for men (35 mmol/mol). This is reflected in the $Z\text{-scores}$, which showed the largest deviation from zero in the <45 years age group (–9.1) and the smallest in the older age group (–2.9).

Conclusion: We showed differences in HbA1c and FPG patterns with age between men and women, with implications for the diabetes diagnostic threshold for HbA1c in pre-menopausal women, the underdiagnosis of type 2 diabetes in younger women, and missed opportunities for intervention. We propose that a suggested change to HbA1c reference ranges in this group warrants serious consideration and detailed evaluation.

Keywords: HbA1c; Fasting glucose; Screening; Men; Women; Menopause

Key Summary Points

Why we carried out the study

We previously reported sex differences in the distribution of glycated haemoglobin (HbA1c) for men/women aged <50 years vs older individuals, with implications for delayed diabetes diagnosis.

Here, we explored whether this pattern was also in matched fasting plasma glucose (FPG) levels in two independent laboratory datasets.

What we learnt from the study

Specifically, we identified, using matched HbA1c and FPG data from two cohorts of primary care non-diabetes patients, that (a) HbA1c is lower in women aged <45 years than men aged <45 years, but not in the 45–55 and ≥55 years age groups; (b) FPG is consistently lower in women than men across all age groups; and (c) both HbA1c and FPG increase with age.

We therefore propose that a suggested change to HbA1c reference ranges in this group warrants serious consideration and detailed evaluation.

INTRODUCTION

We have previously reported that there is a sex differential in the distribution of glycated haemoglobin (HbA1c) levels between men and women aged less than 50 years vs older individuals [1]. This has implications for the delayed diagnosis of type 2 diabetes (T2D) in younger women and their subsequent long-term health [2]. Specifically, in an analysis of over 1 million individuals who had single HbA1c tests at seven NHS trusts across England, we showed that 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 showed that women had a lower HbA1c by 1.6 mmol/mol than men of the same age [1]. This paper builds on the work described in the Holland et al. paper [1], with a different dataset across two UK sites and the analysis now including fasting plasma glucose.

While HbA1c has become a validated easy measure of glycaemic status [3], fasting plasma glucose (FPG) also reflects inherent FPG

dysregulation and is an accepted marker not just of diabetes diagnosis but also for the likelihood of a future diagnosis of type 2 diabetes (T2D) [4, 5].

Although non-diabetic hyperglycaemia (NDH; previously commonly referred to as pre-diabetes) is more often observed in women, fewer women are being diagnosed with type 2 diabetes compared with men [6]. NDH is known to be associated with a higher all-cause mortality in men and women [7]. However, the risk of cardiovascular disease is higher in women with NDH than men with NDH [7], as are mortality rates in women vs men with T2D [8]. At the time of T2D diagnosis, women have a higher risk factor burden, such as obesity [9] and hypertension [10, 11]. These data would support the concept of delayed diagnosis in women compared to men; hence, timely diagnosis is of paramount importance.

There is limited literature in this area. In 2022, Yang et al. [12] reported that HbA1c may underestimate fasting glucose in men compared with women, possibly due to erythrocyte properties. It was highlighted by the authors that HbA1c and liability for diabetes reduce lifespan differentially because diagnostic and management criteria involving HbA1c mean that glycaemia in men is undertreated compared to women, which needs urgent investigation. Furthermore, Ma et al. in 2016 [13] reported gender differences in HbA1c.

Two papers have previously reported a sex disparity in diabetic cardiovascular disease in that, compared to men with diabetes, female patients have a 58% and 8% higher mortality risk for coronary heart disease and stroke, respectively [14, 15]. The extent to which prediabetes and undiagnosed diabetes were associated with the risk of CVD in men and women remains unclear.

We have now had the opportunity to examine, in two laboratory datasets, how FPG relates to HbA1c, sex and age. Our aim in this study was to explore how our previous findings of lower HbA1c levels in younger women than in younger men relate to FPG levels.

METHODS

Patients

We extracted data on HbA1c and FPG levels collected on the same day from the same patient between Jan 2019 and Dec 2023 from clinical biochemistry laboratory databases from Mersey and West Lancashire Teaching Hospitals NHS Trust (MWL; $n = 10,153$) and Cambridge University Hospitals NHS Foundation Trust (CUH; $n = 10,022$).

Data on patient age and sex were also collected. This was a retrospective study.

Only cases from general practice with a single HbA1c test performed during the 3-year period were studied. This was to minimise the risk of including non-diagnostic tests and tests from specialist care (e.g. endocrinology, antenatal services), and it left a final dataset of 17,271 patients. We excluded anyone with known diabetes on the basis of clinical details provided or repeated laboratory testing after an HbA1c result of 48 mmol/mol or more.

Biochemical Analyses

Plasma glucose was measured using either the Siemens Advia 2400 (CUH: Jan 2019–Sept 2022, MWL: Jan 2019–Jan 2020) or Siemens Atellica (CUH: Oct 2022–Dec 2023, MWL: Feb 2020–Dec 2023) platforms, both of which use the hexokinase plus glucose 6 phosphate dehydrogenase methodology.

HbA1c was measured at CUH using either a TOSOH G8 (Jan 2019–Feb 2020) or a TOSOH G11 (Mar 2020–Dec 2023), both of which use an identical ion-exchange high-performance liquid chromatography method. At MWL, HbA1c was measured using a Menarini Premier Hb9210 Resolution (Jan 2019–Jan 2020), which utilises ion-exchange high-performance liquid chromatography technology, and a Sebia Cap3 analyser (Feb 2020–Dec 2023), which is based on a capillary electrophoresis methodology.

For both analytes at each site, comparisons between methods were within acceptable clinical limits.

Data Analysis

We did not perform formal power calculations given the size of the dataset. However, post hoc power calculations on natural-logarithm-transformed data showed that the sample size for each age group for the difference in HbA1c, FPG and the ratio had a power (beta value) of at least 90% at a level of significance (alpha value) of 0.01 for a difference of 0.1 mmol/L for FPG, 1 mmol/mol for HbA1c and 0.1 for the ratio of HbA1c to FPG, including for the smallest age group (45–54 years). However, the interpretation of the importance of the findings was based on clinical as well as statistical significance.

Data were analysed in three ways:

- The trend in median HbA1c and FPG by age, separately in men and women
- The ratio of HbA1c to FPG by age, separately in men and women
- The distribution of HbA1c and FPG values, split by age (<45, 45–54 and ≥55 years), separately in men and women

Analyses were initially performed for the two datasets separately. In light of the similar characteristics of the data from the two sites (Table 1), the final analysis was conducted on the combined cohort. Data were processed in Excel, and statistical analyses were performed using Stata, version 18 (Stata Corporation, TX).

The Mann–Whitney *U*-test was used to compare HbA1c, FPG and the HbA1c:FPG ratio between men and women in the three age groups.

Ethics

As this work represented an evaluation of the respective clinical biochemistry services, local ethics approval from our governance board was obtained at Salford Royal Hospital (reference NCA 2023/13). Patients were given the opportunity to opt out of their data being used. All data were anonymised.

RESULTS

The demographic information for each cohort is shown in Table 1. The mean age of the combined cohort was 51.9 years (52.9% were women). The median (IQR) HbA1c was 37 (34–40) mmol/mol and FPG was 4.9 (4.5–5.4) mmol/L. The MWL cohort was slightly younger than the CUH cohort and had a lower proportion of women.

Age-Related Trends in HbA1c and FPG by Sex

Confirming our previous data, HbA1c levels were lower by ~1 mmol/mol in younger women (aged <45 years) than men in the same age range (Fig. 1a). By the 50–54 years age group, the two trend lines for median HbA1c converged such that the sex difference was not observed in those aged over 55 years (Fig. 1a). As expected, the

Table 1 Patient demographics

	MWL	CUH	Combined
Number of patients	7249	10,022	17,271
Age (years: mean ± SD)	55.3 ± 19.1	49.4 ± 19.2	51.9 ± 19.4
Proportion of females (%)	53.8	52.2	52.9
HbA1c levels (mmol/mol; median & IQR)	38 (35–42)	36 (34–39)	37 (34–40)
FPG levels (mmol/L; median & IQR)	5.0 (4.6–5.7)	4.8 (4.4–5.2)	4.9 (4.5–5.4)

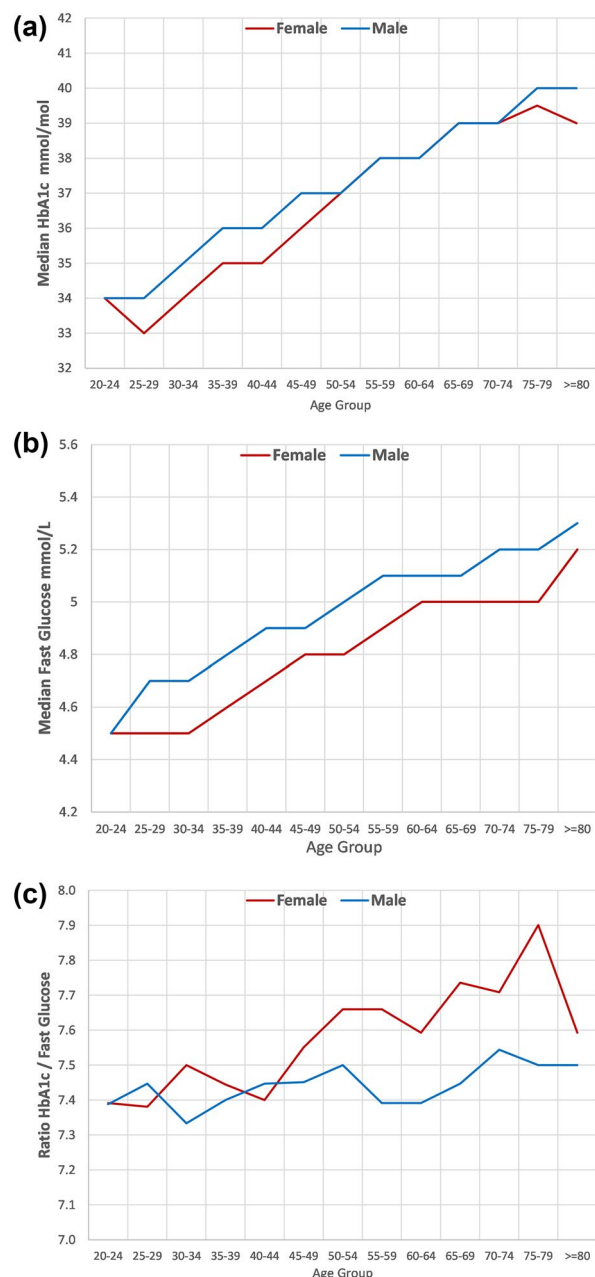


Fig. 1 Age-related trends in median values for **a** HbA1c, **b** FPG and **c** the ratio of HbA1c:FPG split by sex

overall levels of HbA1c increased with age in both groups.

For FPG in these same individuals, levels were higher in women than men across the full age range, with a gap of between 0.1 and 0.2 mmol/L across the age spectrum (Fig. 1b).

The ratio of HbA1c to FPG (Fig. 1c) was broadly similar and relatively constant in men and women aged under 45 years at approximately 7.3–7.5. After the age of 45 years, the ratio in men remained at this level, while that in older women increased year on year, reaching over 7.7 by the age of 65 years (Fig. 1c). If the HbA1c values seen in women aged <45 years were the same as those in women >54 years, the ratio in women aged under 45 years would have ranged from 7.56 to 7.66, which is similar to that seen in older women and consistently higher by ~0.2 than that seen in men.

HbA1c and FPG Distributions by Age Group and Sex

We confirmed our previous findings (Table 2 and Fig. 2a) that, though statistically different (due to the large number of observations), median HbA1c levels in women aged ≥55 years and 45–55 years were the same as in men (39 and 37 mmol/mol, respectively) and that, for women aged <45 years, the median HbA1c (34 mmol/mol) was 1 mol/mol lower than in men (35 mmol/mol). This is reflected in the Z-scores, which showed the largest deviation from zero in the <45 years age group (−9.1) and the smallest in the older age group (−2.9).

We observed that the median FPG (Table 2 and Fig. 2b) for women was 0.1–0.2 mmol/l lower than for men in all three age groups (all $p < 0.001$, Z-scores −7.3 to −10.4). This suggests that the relation between FPG and HbA1c is not consistent between sexes and across age groups. This is reflected in the ratio of HbA1c to FPG (Fig. 2c), which was not significantly different between men and women in the lower age group ($p = 0.649$, Z-score 0.5) but was higher in women in the >55 years age group ($p < 0.001$, Z-score 8.9). The 45–54 years age group showed an intermediate ratio ($p = 0.004$, Z-score 2.9).

DISCUSSION

We here provide evidence that there is a difference in the relation between circulating FPG level and HbA1c with age and in younger

Table 2 Distributions of HbA1c and FPG

Sex		Age < 45 years		Age 45–54 years		Age ≥ 55 years	
		F	M	F	M	F	M
<i>N</i>		3412	2560	1563	1501	4147	4073
HbA1c in mmol/mol	Median (IQR)	34 (32–37)	35 (33–38)	37 (34–39)	37 (35–40)	39 (36–42)	39 (36–43)
	Median difference: F – M	– 1		0		0	
	Z-score	– 9.1		– 4.2		– 2.9	
	<i>P</i> value (M vs F)	< 0.001		< 0.001		0.004	
FPG in mmol/L	Median (IQR)	4.6 (4.3–4.9)	4.7 (4.4–5.1)	4.8 (4.5–5.2)	5.0 (4.6–5.4)	5.0 (4.6–5.6)	5.2 (4.8–5.8)
	Median difference: F – M	– 0.1		– 0.2		– 0.2	
	Z-score	– 9.5		– 7.3		– 10.4	
	<i>P</i> value (M vs F)	< 0.001		< 0.001		< 0.001	
Ratio: HbA1c/FPG	Median (IQR)	7.44 (6.68–8.05)	7.45 (6.86–8.04)	7.61 (6.96–8.14)	7.50 (6.86–8.10)	7.69 (7.00–8.33)	7.45 (6.79–8.14)
	Median difference: F – M	– 0.01		0.09		0.24	
	Z-score	0.5		2.9		8.9	
	<i>P</i> value (M vs F)	0.649		0.004		< 0.001	

women vs younger men, with implications for the diabetes diagnostic threshold. Specifically, we identified, using matched HbA1c and FPG data from two cohorts of primary care non-diabetes patients, that (a) both HbA1c and FPG increase with age, (b) FPG is consistently lower in women than men across all age groups, and (c) HbA1c is lower in women aged < 45 years than men aged < 45 years but not in the 45–55 and ≥ 55 years age groups.

The key message from this study is that our previously identified difference in HbA1c levels in younger women compared to younger men, but not older women and men [1], is not reflected in the FPG levels taken at the same time. This adds weight to our original argument that this may reflect non-physiological, not pathological, factors such as menstruation in pre-menopausal women. While some may argue that this is self-evident and has indeed been identified elsewhere [16–20], it raises important

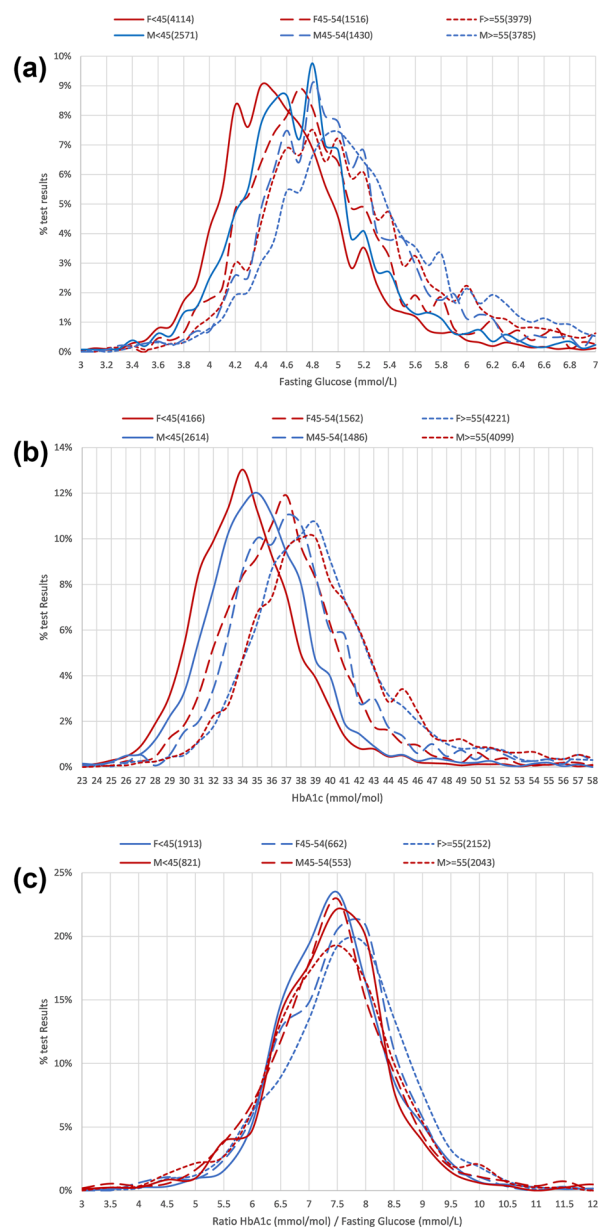


Fig. 2 Distributions of **a** HbA1c, **b** FPG and **c** HbA1c:FPG ratio values split by age group and sex

questions regarding the diagnostic thresholds used for both FPG and, particularly, HbA1c that have hitherto not been addressed.

At face value, these findings might suggest that age- and sex-specific reference ranges should be used for the diagnosis (and potential monitoring) of diabetes mellitus. However, it is important to differentiate age- and sex-related differences in HbA1c and FPG levels arising from

the interaction between physiological (e.g. differences between the sexes in glucose metabolism and its regulation; including the effect of pregnancy), pathological (e.g. decreasing pancreatic function with age) and chemical factors (e.g. factors influencing erythrocyte turnover and hence haemoglobin glycation levels).

Changes in HbA1c and FPG with Age

The increasing concentrations of FPG and HbA1c with age have been previously documented [21–23] and are suggested to reflect decreasing tissue insulin sensitivity and reduced insulin secretion by the pancreas with age [24]. This increase is reflected in the increasing prevalence of diabetes with age [25]. While some have suggested that age-dependent reference ranges should be used [26], we would suggest that this would not be warranted as it is more likely to reflect age-related deterioration of β -cell function, potentially associated with changes in visceral and subcutaneous fat [27, 28], though the molecular mechanisms behind these changes are complex and not fully understood [29]. While it is true that there are non-physiological changes in HbA1c with age, including changes in erythrocyte turnover [26], leading to calls from some to introduce age-specific reference ranges, we propose that age-related differences are likely to reflect important pathological changes and therefore do not warrant age-specific reference ranges.

Differences in FPG Between Men and Women

The finding of lower FPG levels in women than men across all age groups is well known and reflects complex sex-related differences in glucose homeostasis, including interrelated factors such as oestrogen levels, insulin sensitivity, muscle and adipose tissue mass [30]. It is well established that oestrogen acts as an insulin-sensitising agent [31, 32]. It might be expected therefore that this relation between FPG in men and women might change at the menopause. Our data illustrate that this is not the case, with the lower FPG levels being consistently 0.1–0.2

mmol/L lower in women across all ages. It is likely that this consistent difference is a reflection of both physiological and pathological effects, so our view is that there is currently insufficient evidence to recommend sex-specific reference ranges in FPG.

Differences in HbA1c Between Men and Women

Our findings on the age- and sex-related changes in HbA1c are consistent with observations from our previous work and those of other groups, who reported that HbA1c was lower in pre-menopausal women than men of the same age [17–20]. We and others have proposed that these observations may reflect the effect of menstruation in younger women, leading to a shorter mean erythrocyte half-life and hence shorter exposure of haemoglobin to circulating glucose compared with individuals who do not menstruate [33]. The nature of this study as a retrospective laboratory-data-based project precludes any further investigation at this stage in relation to studies of red cell turnover. However, we would argue that the lack of a similar pattern with FPG suggests that this observation is less likely to be due to sex- and age-specific physiological changes such as the effect of oestrogen in the pre-menopausal period [20]. The change in the ratio between HbA1c and FPG with age in women makes this contrast between FPG and HbA1c patterns particularly evident (Fig. 1c). We contest, therefore, that there is a case for sex-specific reference ranges for HbA1c in pre-menopausal women.

Implications of Sex-Specific Reference Ranges for HbA1c in Pre-menopausal Women

Our observations raise the question as to whether the ‘set point’ for HbA1c may be lower in women than in men with the result that female levels of HbA1c that would be considered ‘normal’ for men are actually a reflection

of developing metabolic stress in women. These differences between men and women, together with those due to culture, education, lifestyle and ethnicity, will influence the progression to overt diabetes over time.

Given that the diagnosis of T2D is now largely based on HbA1c, the lack of use of sex-specific reference ranges and a diagnostic cut point for type 2 diabetes for pre-menopausal women could potentially lead to the underdiagnosis of T2D in younger women and missed opportunities for intervention and timely cardiovascular risk reduction intervention [7, 9, 10], which is of relevance given the higher mortality rates in women vs men with T2D [8]. This might contribute to our understanding of why women with diabetes are diagnosed later in life [2] and have a higher mortality rate than men with T2D [8, 34].

We accept that while the reported differences in HbA1c are small, at a population level in relation to screening, many thousands of women would still be affected by a change in the threshold for the diagnosis of T2D.

It might be argued that the 1 mmol/mol difference in HbA1c level in younger women is small and would not warrant such a major change in policy regarding diabetes diagnosis and monitoring. However, as we discussed in our previous paper, the implications at a population level of not implementing this change are significant [1].

Limitations

Limitations of our study include that it only involved two UK laboratories. Nevertheless, a large number of parallel samples in relation to paired HbA1c and FPG collected on the same day were analysed. Furthermore, we have previously shown that the pattern of HbA1c with age and gender was consistent across seven laboratories when analysed separately [1]. This was also the case when the sites considered in this study were analysed separately (data not shown). We therefore believe that our findings are representative of the UK population. Furthermore, similar

patterns have been seen in other populations [12–16].

The between-sex difference could be exaggerated by the large sample size. However, we would emphasise that the aim of this paper is not to change the guidance but rather to raise a question about whether the reference range for younger women is correct, with the suggestion that this matter merits further evaluation.

As we examined laboratory data here, not primary care data, information about the full medical history, including a family history of diabetes and physical characteristics, is not available. Such an evaluation would require access to primary care records. A strength of this study is that because we have used laboratory data, we can be certain that all the tests done for HbA1c and fasting glucose were done in the context of screening for type 2 diabetes rather than the monitoring of already diagnosed type 2 diabetes and were done on the same day.

Our dataset included matched FPG and HbA1c samples based on primary care patients with a single HbA1c sample over a 3-year period. While this would minimise the likelihood of including people with diabetes or being tested for gestational diabetes, it is possible that some such patients would have been included. However, the proportion of these is likely to be small and therefore they are unlikely to change the overall conclusions of the study. Similarly, while the sampling may include some pregnant women and people with other conditions affecting HbA1c and/or FPG levels (such as anaemia), these are unlikely to affect the patterns seen to any significant degree. An important limitation of the study regarding diabetes diagnostic thresholds is the absence of most of the confounding variables that may affect the results.

CONCLUSION

In conclusion, we provide additional evidence that there is a differential in the relation between FPG level and HbA1c in younger women vs younger men, with implications for the diabetes diagnostic threshold in pre-menopausal women, potentially leading to the underdiagnosis of type

2 diabetes in these women and missed opportunities for intervention.

We propose that this suggested change to HbA1c reference ranges in this group warrants serious consideration, particularly given the higher mortality for diabetes in women.

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Author Contributions. Design: Mike Stedman, David Holland, Adrian Heald, Pensee Wu and Anthony Fryer devised the original concept. Conduct/data extraction: Mike Stedman, David Holland, Lewis Green, Ian Halsall and Anthony Fryer were responsible for the extraction and initial cleaning of the data from laboratory records. Analysis: Anthony Fryer and Mike Stedman performed the data manipulation and analysis. Pensee Wu, Fahmy Hanna, Adrian Heald, Martin Gibson, Kashyap Patel and Anthony Fryer provided the interpretation of the analysis. Writing the manuscript: Adrian Heald and wrote the initial draft of the paper, which was then critiqued by all other authors as part of regular team meetings and the manuscript revision process, with helpful critique from Jonathan Scargill and Kashyap Patel. All authors approved the final version of the manuscript.

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Data Availability. Data are available from the corresponding author on reasonable request.

Declarations

Conflict of Interest. Mike Stedman, Adrian H. Heald, David Holland, Ian Halsall, Lewis Green, Pensee Wu, Kashyap Patel, Jonathan Scargill, Martin Gibson, Fahmy W.F. Hanna, and Anthony A. Fryer have no conflicts of interest to declare.

Ethical Approval. Local ethics approval from our governance board was obtained at Salford Royal Hospital reference NCA 2023/13. Patients were given the opportunity to opt out of their data being used. All data were anonymised.

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