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ARTICLE

Dysglycaemia and the risk of acute myocardial infarction in multiple ethnic groups: an analysis of 15,780 patients from the INTERHEART study

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Abstract
Aims/hypothesis Although diabetes is an established risk factor for myocardial infarction (MI), disease control may vary. HbA_{1c} is a reliable index of ambient glucose levels and may provide more information on MI risk than diabetes status.
Methods The relationship between HbA_{1c} levels in MI patients and controls who participated in the 52 country INTERHEART study was analysed.
Results In 15,780 participants with a HbA_{1c} value (1,993 of whom had diabetes), the mean (SD) levels for HbA_{1c} were 6.15% (1.10) in the 6,761 MI patients and 5.85% (0.80) in the control participants. After adjustment for age, sex and nine major MI risk factors (including diabetes), higher HbA_{1c} fifths above the lowest fifth (HbA_{1c} <5.4%) were associated with progressively higher OR of MI, with OR for the highest HbA_{1c} fifth (≥6.12%) being 1.55 (95% CI 1.37–1.75). When analysed as a continuous variable after adjustment for the same factors, every 1% higher HbA_{1c} value was associated with 19% (95% CI 14–23) higher odds of MI, while every 0.5% higher HbA_{1c} was associated with 9% higher odds of MI (95% CI 7–11). Concordant relationships were noted across subgroups, with a higher OR noted in younger people, patients without diabetes or hypertension, and those from some regions and ethnicities.

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Conclusions/interpretation The HbA_{1c} value provides more information on MI odds than self-reported diabetes status or many other established risk factors. Every 1% increment independently predicts a 19% higher odds of MI after accounting for other MI risk factors including diabetes.

Keywords Case–control · Diabetes · Dysglycaemia · Glycated haemoglobin · Myocardial infarction

Abbreviations

Apo Apolipoprotein
MI Myocardial infarction

Introduction

Diabetes is a common chronic condition of increasing prevalence, which currently affects approximately 5% of adults worldwide and up to 10% of adults in western populations [1–3]. An even larger proportion of individuals is affected by lesser degrees of dysglycaemia, including impaired glucose tolerance and/or impaired fasting glucose. Many epidemiological studies have reported that progressively higher fasting [4, 5] or post-load [6, 7] glucose or HbA_{1c} levels [8–10] predict a progressively higher incidence of cardiovascular outcomes. For example, in a recent large prospective epidemiological study of 10,032 individuals, in which only 2.4% (243) of participants had known diabetes and 5.5% (549) had either known diabetes or $HbA_{1c} \geq 6.5\%$, a 1% higher HbA_{1c} level above 5% predicted a 20% higher incidence of cardiovascular disease after controlling for diabetes and several cardiovascular risk factors [8]. Another epidemiological study [9] reported that a 1% higher HbA_{1c} predicted a 14% higher incidence of cardiovascular outcomes in people with diabetes and a 68% higher incidence in people without diabetes. Consistent with these observations is the high prevalence of dysglycaemia observed in people presenting with an acute myocardial infarction (MI). Thus, approximately two thirds of individuals presenting to a coronary care unit have diabetes, impaired glucose tolerance or impaired fasting glucose based on glucose tolerance testing [11, 12].

The INTERHEART Study was an international case–control study of MI conducted in 29,972 people in 52 countries [13]. This study reported that nine cardiovascular risk factors confer more than 90% of the population-attributable risk of MI globally. After accounting for other risk factors, self-reported diabetes was independently associated with an OR of 2.37 (95% CI 2.07–2.71) and a population-attributable risk of 10%. However, this is likely to be an underestimate of the importance of dysglycaemia as a risk factor for MI, as prevalent diabetes is often undiagnosed and abnormal glucose values at the time of an MI may be dismissed as being due to stress and as not reflecting an underlying metabolic abnormality. Moreover, little is known about the relationship between MI and dysglycaemia in multiple ethnic groups and regions across the world.

At the time that the INTERHEART study was conducted, blood samples for HbA_{1c} levels were collected in approximately 50% of all participants. Here we report on whether HbA_{1c} level is a cardiovascular risk factor that is independent of self-reported diabetes status, as well as independent of age, sex and the other eight major global cardiovascular risk factors identified in the INTERHEART study. We also report on the relationship between HbA_{1c} level and risk of MI within subgroups of individuals defined by clinical characteristics, ethnicity or geographic region.

Methods

Participants The design and key results of the INTERHEART study have been previously published [13]. Briefly, this was a large, international, standardised case–control study of 15,152 MI patients and 14,820 controls. The patient group comprised people from 262 sites in 52 countries worldwide (webtable 1 available from http://image.thelancet.com/extras/04art8001webtable1.pdf [13]), who were admitted within 24 h of their first acute MI. At least one sex- and age-matched control with no history of heart disease or exertional chest pain was recruited for each case. All participants provided informed consent. Both patient and control groups were interviewed and examined and asked to provide non-fasting blood samples.

Procedures Findings from structured questionnaires and physical examinations were transferred to the Population Health Research Institute at McMaster University and Hamilton Health Sciences in Hamilton, ON, Canada. The presence of diabetes and/or hypertension was based on self-report and ethnic origin was self-identified. Any tobacco smoking within the prior 12 months was defined as current smoking. Waist and hip circumference were measured using a non-stretchable tape at the narrowest point between the costal margin and iliac crest, and at the level of the greater trochanter respectively. Thirds of abdominal obesity for men and for women were based on WHR. Cutpoints for each third for each sex were determined from the control data and were ≤0.83, 0.84–0.90 and >0.90 for women, and ≤0.90, 0.91–0.95 and >0.95 for men; abdominal obesity was defined as a measurement in the top third for each sex. Individuals were judged to be physically active if they were regularly involved in moderate (walking, cycling or

Table 1 The prevalence of diabetes and high HbA_{1c} levels in MI patients and controls

Variable	Total	Cases	Controls
n	15,780	6,761	9,019
Diabetes	1,993 (12.6)	1,293 (19.1)	700 (7.8)
HbA_{1c}≥6.12%	4,089 (25.9)	2,208 (32.7)	1,881 (20.9)
With diabetes	1,304 (8.3)	872 (12.9)	432 (4.8)
Without diabetes	2,785 (17.6)	1,336 (19.8)	1,449 (16.1)
HbA_{1c}≥5.8%	7,737 (49.0)	3,771 (55.8)	3,966 (44.0)
With diabetes	1,582 (10.0)	1,049 (15.5)	533 (5.9)
Without diabetes	6,155 (39.0)	2,722 (40.3)	3,433 (38.1)

Data are presented as *n* (%) unless stated otherwise

gardening) or strenuous (jogging, football and vigorous swimming) exercise for ≥4 h per week. Regular alcohol use was defined as self-reported consumption at least once per week. Daily consumption of fruits and vegetables was defined as daily intake of both.

Non-fasting blood samples were available in 21,508 (79%) of MI patients and controls, and were analysed centrally as reported previously. Samples (20 ml) were drawn within 24 h of symptom onset for two-thirds of the MI patients and after 24 h for the remainder; they were then centrifuged at 1,500 *g*, separated and frozen at −20°C to −70°C. At the same time, additional samples of whole blood were collected on filter paper specifically designed for analysis of capillary or venous whole-blood samples [14]. HbA_{1c} was analysed centrally in Canada and China using a HPLC system (Variant II; Bio-Rad, Munich Germany) standardised to the Diabetes Control and Complications Trial assay. Both laboratories have received National Glycohemoglobin Standardization Program (NGSP) Level 1 certification for this method. The inter-assay imprecision for the low and high whole-blood and the low and high filter paper controls was less than 2%. Fifths of HbA_{1c} were based on the distribution of HbA_{1c} levels in controls without a history of diabetes.

Apolipoproteins (Apo) A-1 and B were measured using a device (Hitachi 917; Roche Diagnostics, Mannheim, Germany) and the ApoB version 2 and ApoA-1 version 2 kits (Tina-quant; Roche). The same measurement kits and a Hitachi 911 analyser (Roche) were used in Beijing, China. The two laboratories were further standardised by measuring the same lot numbers of Precinorm and Precipath controls from Roche Diagnostics in every run. In every run of patient sample analyses in China, two study patients and two reference pool samples were measured from samples that had been previously analysed in the central core laboratory in Canada [15].

Statistical analyses The rate or mean value of risk factors within different fifths of HbA_{1c} (defined above) were calculated and tests for trends across fifths of HbA_{1c} for MI patients and for controls were done using the Cochran–Armitage test for categorical variables and the linear trend test for continuous variables.

Table 2 Distribution of risk factors in control participants across fifths of HbA_{1c} levels

Variable	Fifths of HbA_{1c} levels (%)					
	<5.4	5.4–5.59	5.6–5.79	5.8–6.11	≥6.12	*p* value
N	1,768	1,509	1,776	2,085	1,881	
Mean age (years)	54.5±12.5	55.7±12.3	56.0±12.1	58.2±11.8	59.2±11.3	<0.0001
Men, *n* (%)	1,384 (78.3)	1,168 (77.4)	1,419 (79.9)	1,565 (75.1)	1,309 (69.6)	
Women, *n* (%)	384 (21.7)	341 (22.6)	357 (20.1)	520 (24.9)	572 (30.4)	<0.0001
Diabetes, *n* (%)	35 (2.0)	53 (3.5)	79 (4.5)	101 (4.9)	432 (23.0)	<0.0001
Hypertension, *n* (%)	307 (17.4)	300 (19.9)	384 (21.7)	567 (27.3)	539 (28.7)	<0.0001
Current smoking, *n* (%)	545 (31.2)	461 (31.2)	489 (27.8)	565 (27.4)	447 (24.2)	<0.0001
Physically active ≥ 4 h/week, *n* (%)	322 (18.2)	295 (19.6)	371 (20.9)	445 (21.4)	329 (17.5)	0.89
Daily fruit and vegetable intake, *n* (%)	701 (40.3)	629 (42.3)	732 (41.8)	885 (43.0)	861 (46.5)	0.0004
Alcohol use ≥ once/week, *n* (%)	436 (24.8)	418 (27.9)	449 (25.4)	515 (24.8)	416 (22.2)	0.013
Abdominal obesity (WHR top 3rd), *n* (%)	498 (28.7)	485 (32.7)	579 (33.3)	708 (34.5)	709 (38.5)	<0.001
Mean BMI	25.4±4.0	25.9±4.1	26.0±4.2	26.1±4.1	26.5±4.5	<0.0001
Mean ApoB/ApoA1	0.75±0.30	0.78±0.26	0.80±0.28	0.82±0.30	0.84±0.31	<0.0001

Unless otherwise indicated, values are mean ± SD

HbA_{1c} categories were derived from dividing the non-diabetic control participants into five groups by quintiles. The denominator varies slightly by row and cell reflecting missing data

p values are for significance of trend across fifths using Cochran–Armitage test

The odds and 95% CIs of suffering a MI in the 2nd, 3rd, 4th and 5th highest fifths of HbA_{1c} compared with the lowest fifth, after controlling for other risk factors, were calculated using unconditional logistic regression as described previously [13], with case status as the dependent variable and fifth of HbA_{1c} as well as other risk factors as independent variables. The proportion of MI cases (and 95% CIs) vs HbA_{1c} were plotted for: (1) all participants; (2) participants with no diabetes history; and (3) participants with no diabetes history and HbA_{1c}<6.5%; plotting was done using cubic B-spline fits with three HbA_{1c} knots: 5.5%, 6.0% and 6.5%. ORs adjusted for age, sex, region and all of the INTERHEART risk factors (and 95% CIs) were computed and plotted for each of the above groups using cubic B-spline fit and HbA_{1c}≤5.25% as a reference. Logistic regression was used to calculate the odds of being a MI case for every 1% higher HbA_{1c} level within various subgroups and after adjustment for other risk factors. Interaction terms were included as independent variables where appropriate. For models that adjusted for all of the INTERHEART risk factors [13], the risk factors were defined as: (1) history of diabetes; (2) history of hypertension; (3) smoking (classified as never, former or current); (4) daily fruit or vegetable consumption (classified as neither, fruits or vegetables, and fruits and vegetables); (5) WHR thirds according to sex; (6) regular physical activity; (7) regular alcohol use (defined as at least one drink/week); (8) ApoB and ApoA1 thirds; and (9) psychosocial factors based on an index using measures of depression, financial stress, locus of control, global stress and stressful events [16].

Statistical analyses were done using SAS version 9.1 (SAS, Cary, NC, USA). All statistical tests of hypotheses are two sided.

Results

Baseline characteristics of INTERHEART participants including self-reported diabetes status have been published previously [13]. An HbA_{1c} level was available in 15,780 participants (1,993 with self-reported diabetes), comprising 6,761 MI cases (42.8%) and 9,019 controls (57.2%) with mean (SD) HbA_{1c} levels of 6.15% (1.10) and 5.85% (0.80) respectively. For 11,318 individuals, blood for HbA_{1c} measurement was either not sent to the central labs or could not be analysed. Compared with participants without HbA_{1c} value, MI patients and controls with an HbA_{1c} value had a slightly higher BMI and ApoB/ApoA levels. MI patients with an HbA_{1c} value had a 2% higher prevalence of diabetes and 2.4% lower prevalence of hypertension, while controls with an HbA_{1c} had a 4.6% higher prevalence of male sex, a 3.6% higher prevalence of hypertension and a 0.5% higher prevalence of smoking. As noted in Table 1, 1,293 MI cases (19.1%) and 700 controls (7.8%) with an HbA_{1c} level had diabetes; however, 2,208 (32.7%) MI cases and 1,881 (20.9%) controls had HbA_{1c} levels in the top fifth (≥6.12%) and 3,771 (55.8%) MI cases and 3,966 (44.0%) controls had high HbA_{1c} levels ≥5.8%. Interestingly, 1,336 cases (19.8%) and 1,449 controls (16.1%) had an HbA_{1c} level ≥6.12% with no history of diabetes, while 2,722 cases (40.3%) and 3,433 controls (38.1%) had an HbA_{1c} level ≥5.8% with no history of diabetes.

The distribution of cardiovascular risk factors in control participants across HbA_{1c} levels is shown in Table 2. Progressively higher HbA_{1c} levels were associated with increasing age (p<0.0001), BMI (p<0.0001), ApoB/

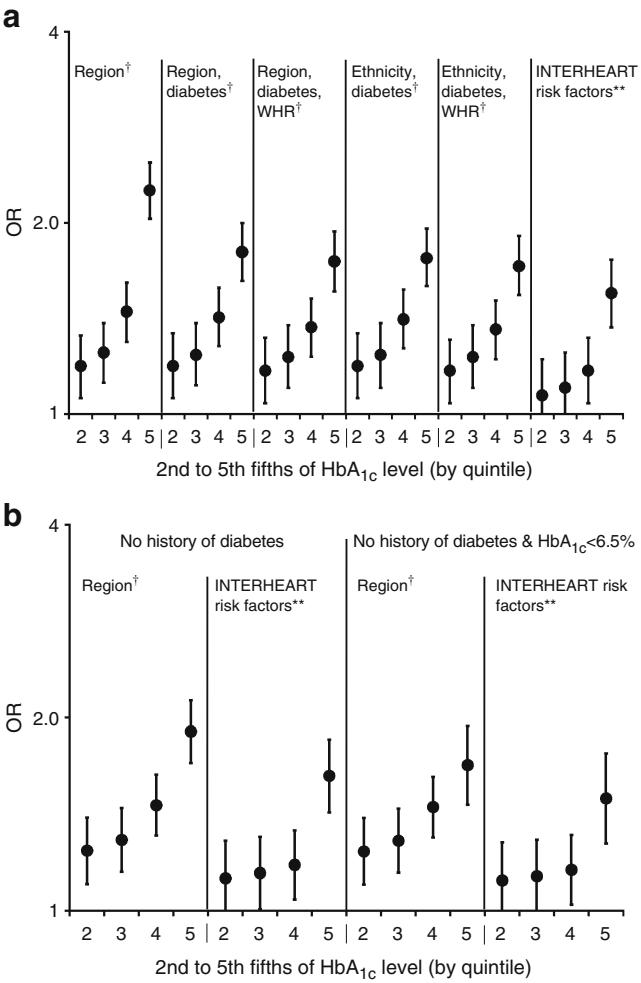

Fig. 1 The ORs (95% CI) of having had an MI (i.e. being a case vs control) within each fifth of HbA1c level in comparison with the lowest fifth, after adjustment for age, sex and various groups of other covariates are shown for all participants (**a**) and for those without diabetes (**b**). The p value for trend across fifths in each model was: **p=0.01 and †p<0.0001. HbA_{1c} categories based on quintiles in the control participants were <5.4%, 5.4–5.59%, 5.6–5.79%, 5.8–6.11% and ≥6.12%

ApoA1 levels ($p<0.0001$). Proportionally more women ($p<0.0001$), people with diabetes ($p<0.0001$), hypertension ($p<0.0001$), fruit and vegetable intake ($p=0.0004$) and abdominal obesity ($p<0.001$), as well as proportionally fewer smokers ($p<0.0001$) and people with regular alcohol consumption ($p=0.013$) also had progressively higher HbA_{1c} levels. No relationship with physical activity was noted ($p=0.9$).

The odds of having suffered an MI vs control in higher HbA_{1c} fifths vs the lowest fifth after adjustment for age, sex and other risk factors for MI are illustrated in Fig. 1a for all participants and in Fig. 1b for participants without diabetes. Incrementally higher fifths of HbA_{1c} were significantly associated with higher odds of being an MI patient in all of the models assessed. Table 3 lists the adjusted odds of having an MI in: (1) the top four HbA_{1c} categories; and (2) the highest HbA_{1c} category in relation to the lowest HbA_{1c} category in all participants overall and within each geographical region, and in participants with no diabetes as well as in those with no diabetes and $HbA_{1c}<6.5\%$. Even after adjustment for all of the INTERHEART risk factors (including diabetes), people in the highest HbA_{1c} category were 1.55 times more likely (95% CI 1.37–1.75) to have an MI than those in the lowest HbA_{1c} category; a similar estimate was observed for analyses that excluded people without diabetes and an $HbA_{1c}<6.5\%$.

The relationship between HbA_{1c} as a continuous variable and both the prevalence and odds of MI for all participants and for participants without evidence of prior diabetes is shown using spline models in Fig. 2. Figure 3 illustrates the estimate of the relationship between the risk of an MI and progressively higher HbA_{1c} levels. Thus, as noted in Fig. 3, every 1% higher HbA_{1c} level was associated with a 40% higher (95% CI 35–45) odds of MI after adjustment for age, sex and region only, and with a 25% higher (95% CI 20–30) odds of MI after additional adjustment for diabetes status. This progressive relationship persisted but was attenuated to 19% (95% CI 14–23) after adjustment for all of the INTERHEART risk factors. When expressed per smaller increment in HbA_{1c}, every 0.5% higher HbA_{1c} level was associated with an 18% (95% CI 16–20), 12% (95% CI 10–14) and 9% higher odds of MI (95% CI 7–11) after adjustment for: (1) age, sex and region; (2) these variables plus diabetes status; and (3) these variables plus all of the remaining INTERHEART risk factors respectively. The relationship also persisted within subgroups defined by the presence or absence of each of the INTERHEART risk factors (Fig. 4a). Moreover, as noted in Fig. 4a, there was a stronger association between MI and HbA_{1c} in people who were younger vs older ($p=0.0001$ for heterogeneity), in the absence of a history of self-reported diabetes ($p=0.009$ for heterogeneity) and in the absence of a history of hypertension ($p=0.02$ for heterogeneity).

The HbA_{1c} level was progressively associated with the odds of MI throughout most regions and ethnicities (Table 3, Fig. 4b), although the strength of the relationship varied somewhat across groups ($p<0.0001$ for heterogeneity). Thus, as noted in Fig. 4b, the relationship between MI and HbA_{1c} was strongest in western Europe than in other regions, and strongest in people of European, Asian, South Asian and Arab ancestry compared with other ancestries.

Table 3 ORs (95% CI) for MI and HbA_{1c} by region

Region	HbA_{1c}	Top 4 HbA_{1c} categories vs lowest, adjusted for:			Top HbA_{1c} category vs lowest adjusted for:		
	Mean (SD)	Age, sex	Age, sex+IH[a]	Age, sex+IH[b]	Age, sex	Age, sex+IH[a]	Age, sex+IH[b]
Overall[c]	5.98 (0.95)	1.55 (1.42–1.70)	1.30 (1.18–1.44)	1.22 (1.10–1.35)	2.25 (2.04–2.50)	1.84 (1.63–2.07)	1.55 (1.37–1.75)
Western Europe	5.93 (0.72)	1.47 (1.01–2.12)	1.26 (0.82–1.93)	1.19 (0.77–1.83)	2.07 (1.36–3.14)	2.01 (1.24–3.26)	1.72 (1.06–2.81)
Central/Eastern Europe	5.87 (0.79)	1.91 (1.47–2.48)	1.56 (1.17– 2.07)	1.46 (1.10–1.95)	2.32 (1.68–3.20)	1.62 (1.13–2.31)	1.31 (0.91–1.87)
Middle East/Egypt	6.12 (1.13)	2.54 (2.06–3.12)	2.30 (1.80–2.93)	2.06 (1.61–2.63)	4.18 (3.31–5.29)	4.07 (3.07–5.38)	3.24 (2.44–4.30)
Africa	6.00 (0–73)	1.78 (1.07–2.95)	1.05 (0.58–1.87)	1.01 (0.56–1.83)	1.82 (1.05–3.14)	0.91 (0.48–1.71)	0.86 (0.45–1.64)
South Asia	6.00 (0.87)	1.29 (0.97–1.72)	1.07 (0.77–1.48)	1.00 (0.72–1.39)	1.79 (1.29–2.47)	1.44 (0.99–2.10)	1.25 (0.86–1.83)
China/Hong Kong	5.98 (1.07)	1.11 (0.94–1.31)	0.94 (0.79–1.13)	0.93 (0.77–1.12)	1.60 (1.31–1.95)	1.31 (1.05–1.62)	1.20 (0.96–1.49)
SE Asia/Japan	6.00 (1.98)	3.30 (2.27–4.77)	2.85 (1.88–4.33)	2.51 (1.65–3.82)	5.49 (3.65–8.25)	4.73 (2.97–7.55)	3.72 (2.32–5.96)
Australia/New Zealand	5.83 (0.52)	0.94 (0.51–1.74)	0.96 (0.49–1.89)	0.91 (0.46–1.78)	1.46 (0.72–2.96)	1.41 (0.65–3.08)	1.26 (0.58–2.75)
South America/Mexico	5.95 (0.91)	1.03 (0.82–1.29)	0.86 (0.65–1.13)	0.78 (0.59–1.03)	1.56 (1.19–2.04)	1.23 (0.88–1.70)	0.95 (0.68–1.33)
North America	5.80 (0.71)	2.33 (1.04–5.20)	1.76 (0.66–4.71)	1.68 (0.63–4.51)	1.82 (0.62–5.32)	1.18 (0.32–4.43)	0.92 (0.24–3.53)
No DM	5.83 (0.76)	1.46 (1.34–1.61)	1.25 (1.13–1.39)	N/A	1.90 (1.70–2.13)	1.62 (1.43–1.85)	N/A
No DM + $HbA_{1c}<6.5\%$	5.64 (0.40)	1.38 (1.25–1.51)	1.18 (1.06–1.31)	N/A	1.69 (1.46–1.94)	1.50 (1.27–1.76)	N/A

[a] INTERHEART risk factors (except diabetes); [b] INTERHEART risk factors (with diabetes); [c] overall estimates are also adjusted for region

DM, diabetes mellitus; N/A, not available

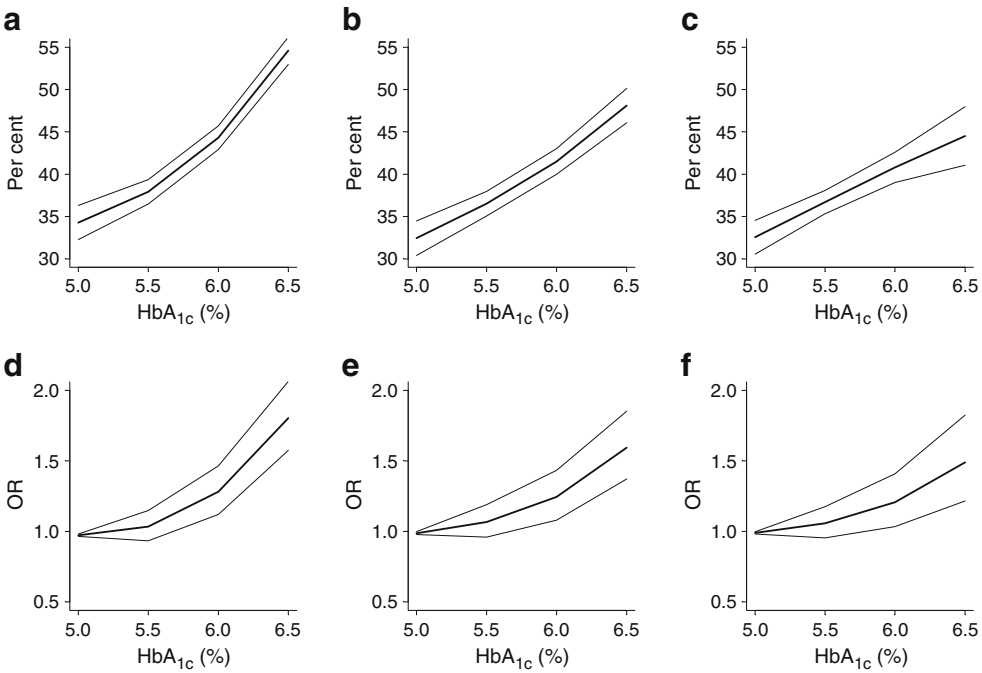

Fig. 2 Spline plots of the per cent of cases and 95% CIs for all participants (**a**); participants with no diabetes history (**b**); and participants with no diabetes history and an HbA_{1c} <6.5% (**c**). Spline plots of ORs and 95% CIs adjusted for age, sex, region, and all of the INTERHEART risk factors are shown in panels **d**, **e** and **f** for these three participant groups, respectively

Discussion

This large global study of 15,780 people demonstrates that objective measurement of dysglycaemia (the HbA_{1c}) is an independent cardiovascular risk factor within all regions of the world and within most ethnic groups. The observation that a 1% higher HbA_{1c} was associated with a 40% higher odds of MI after controlling for age, sex and region, and a 19% higher odds after controlling for all of the INTERHEART risk factors, including diabetes also demonstrates that self-reported diabetes underestimates the association between dysglycaemia and cardiovascular risk. The importance of dysglycaemia as a risk factor for MI in the general population is further highlighted by the finding that after accounting for age, sex, region and all of the INTERHEART risk factors including diabetes, an HbA_{1c} value of ≥5.4% was associated with a 22% higher odds of MI than a lower HbA_{1c}. The observation of a 25% higher odds of MI in people with no history of diabetes and an 18% higher odds in people with both no diabetes history and an HbA_{1c} <6.5% (Table 3) further highlights the relevance of these findings to the general population.

This analysis identified HbA_{1c} as an independent risk factor for MI in the presence of every other independent cardiovascular risk factor as determined by the INTERHEART study, and across most geographical regions and ethnicities. This, and the fact that the ORs remained significant after accounting for all of the INTERHEART risk factors without diabetes and were only slightly attenuated by including diabetes in the model, means that: (1) dysglycaemia increases cardiovascular risk through a mechanism that appears to be independent of these other cardiovascular risk factors; and (2) that this mechanism is relevant with and without a history of diabetes, and operates on a global level.

These findings are consistent with the high prevalence of diabetes, impaired glucose tolerance or impaired fasting glucose observed in people presenting with a suspected MI [11, 12]. As HbA_{1c} levels reflect chronic and not acute glucose elevation, these findings are also consistent with evidence that the abnormal glucose levels at the time of an MI reflect a prior underlying glucose-related abnormality

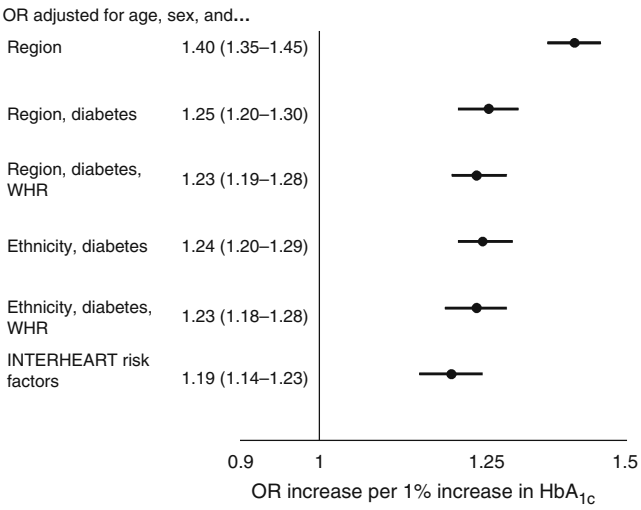

Fig. 3 ORs (95% CI) of having had an MI (i.e. being a case vs control) for every 1% increase in HbA_{1c} after adjustment for age, sex and the other covariates as indicated

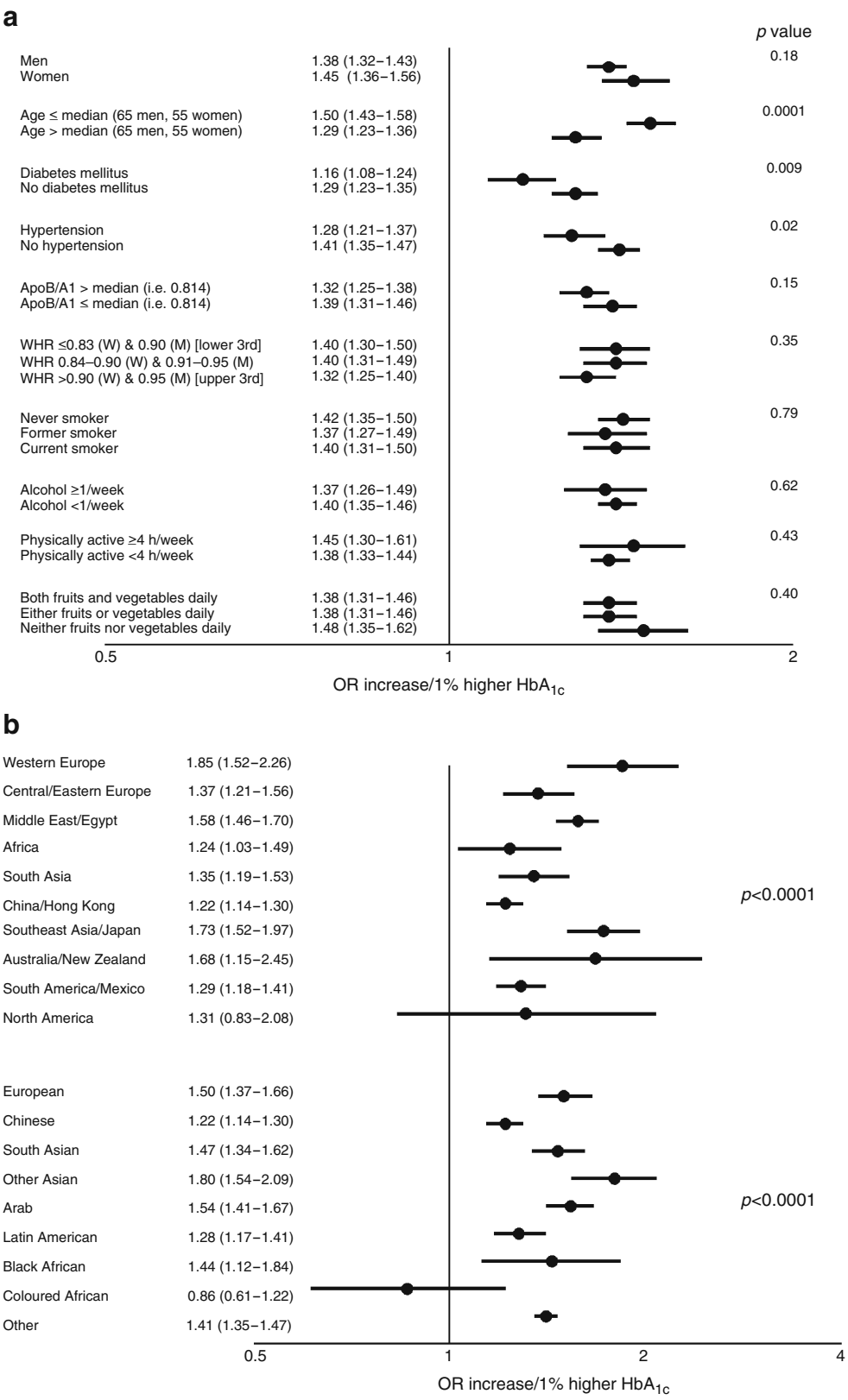

Fig. 4 **a** Age-, sex- and region-adjusted ORs (95% CI) of having had an MI (i.e. being a case vs control) for every 1% increase in HbA_{1c} within various subgroups. For WHR, the lowest, middle and highest thirds were ≤0.90, 0.91–0.95 and >0.96 for men (M) and ≤0.83, 0.84–0.90 and >0.90 for women (W). The *p* values are provided as evidence of heterogeneity across subgroups. **b** Age- and sex-adjusted ORs (95% CI) by geographic region and by self-identified ethnicity

that was present before the event and are not just a response to the MI [17].

Consistent with other epidemiological analyses in the general population and in people with chronic heart failure [9, 10, 18] a higher OR linked the HbA_{1c} value and MI in people with no history of diabetes vs those with such a history. Such an observation may be due to the use of HbA_{1c} as a therapeutic target in people with diabetes. This means that it reflects ambient glucose levels and the effects of treatment (which may modify the relationship between glycaemia and cardiovascular risk), whereas in people without diabetes (in whom HbA_{1c} levels are not typically measured) HbA_{1c} levels just reflect the impact of ambient glucose levels. Alternatively, people with a history of diabetes may receive other therapies that modify the relationship between the HbA_{1c} value and cardiovascular risk. The weaker relationship between HbA_{1c} and MI in the presence of other risk factors such as hypertension and older age, and the observation that adjustment for the INTERHEART risk factors attenuated, but did not eliminate the relationship suggests that these risk factors only partially assess similar underlying cardiovascular pathologies.

These findings are limited by the fact that they were cross-sectional in nature and that HbA_{1c} was not available in all participants. However, the strength inherent in its large sample size, its common approach for measuring cardiovascular risk factors globally and the availability of blood to analyse HbA_{1c} levels mean that these results are a robust estimate of the relationship between dysglycaemia and MI. It is possible that this relationship is due to confounding of dysglycaemia with unmeasured cardiovascular risk factors. However, the fact that it is independent of the INTERHEART risk factors (including self-reported diabetes) highlights its importance. Finally, it is not known whether therapies directed at lowering HbA_{1c} levels can affect prognosis in people presenting with a MI.

In summary, these findings clearly show that dysglycaemia as measured by the HbA_{1c} level in people with or without a history of diabetes is a strong, independent cardiovascular risk factor throughout different regions of the world and ethnicities. Overall, after accounting for the other major cardiovascular risk factors, for every 0.5% and 1% higher HbA_{1c} there was a 9% and 19% higher odds of MI respectively. The findings suggest that dysglycaemia is closely linked to an unmeasured causal factor, and that therapeutic and/or population-based strategies that reduce the prevalence of dysglycaemia by preventing or reversing diabetes, or by slowing the rise of HbA_{1c} with time may reduce the global burden of MI. Indeed, at least three large ongoing clinical trials are currently assessing the effect of preventing diabetes and/or of treating early diabetes on cardiovascular outcomes [19–21], and results from recently reported large trials of glucose lowering have suggested a 17% reduction in MI [22, 23] despite mixed effects on other cardiovascular outcomes including cardiovascular death. Regardless of the results of these and other clinical trials [24], the data presented here highlight the importance of the HbA_{1c} as an important and robust independent risk factor for MI in the presence and absence of a history of diabetes.

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