Type 2 diabetes in migrant South Asians: mechanisms, mitigation and management

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Summary

South Asians, particularly when living in high-income countries, are at significantly elevated risk of type 2 diabetes compared to white Europeans, and typically develop the disease 5-10 years earlier and at a lower body mass index. Migrant South Asians appear more insulin resistant than white Europeans across the life-course and potentially experience beta cell exhaustion at an earlier age. Current evidence suggests that differences in both adiposity (higher percent body fat, greater proportion of deep subcutaneous and visceral fat) and skeletal muscle (lower percent lean mass, lower cardiorespiratory fitness) are likely to contribute. There is currently no clear evidence for genetic factors making a major contribution to South Asians increased diabetes but epigenetic factors may play a role. Regardless of future mechanistic discoveries, South Asians need to be encouraged and helped (via multiple, culturally efficient methods) to maintain high physical activity levels and lower body weights across the life-course to prevent diabetes. In clinical terms, cardiovascular risks have attenuated over time in migrant South Asians with diabetes but retinopathy and renal complication risks remain high due to their higher levels of glycaemia and more rapid glycaemic deterioration over time. We critically review these aspects and suggest areas for future research.

Key messages Panel

Proposed guidance/recommendations for clinicians and public health officials

- Migrant South Asians have a 2-4 fold higher risk of diabetes independent of adiposity, and develop diabetes on average 5-10 years earlier compared with white Europeans. This excess risk is best captured in country or region-specific diabetes risk scores which include ethnicity as a predictor.
- Screening for diabetes (using HbA1c or fasting glucose) in South Asians should either be guided by ethnicity-specific risk scores or be initiated at lower BMI levels in than in white Europeans
- To mitigate such risks, migrant South Asians should have their excess risk explained in an accessible manner and encouraged to maintain lower body weights and higher physical activity levels throughout the life course.
- Current activity levels in migrant South Asians are low. Thus innovative culturally appropriate interventions to increase physical activity need to be developed and implemented for both South Asian males and females.
- South Asians appear to progress more rapidly from 'pre-diabetes' to diabetes than white Europeans, and current lifestyle interventions are less effective at preventing the transition from 'pre-diabetes' to diabetes in South Asians. Thus, lowering the 'pre-diabetes' threshold for the initiation of intervention from 6.0% to 5.7% and/or more intensive lifestyle intervention may be needed for diabetes prevention in South Asians.
- Once diabetes is diagnosed, migrant South Asians have more rapid deterioration in glycaemic control. Thus greater efforts to manage the hyperglycaemia by encouraging (more) intensive lifestyle changes or, if this fails, earlier escalation in oral therapies is needed to mitigate against higher microvascular risks. Wherever possible, early diabetes consultations should include health care workers speaking in the patient's native language.
- Trials testing efficacy of differing glycaemia-lowering medications in South Asians are also lacking and would also be useful.
- Early prescription of ACE/ARB medications in migrant South Asians newly diagnosed with diabetes may be advantageous with a target of <130/80 to mitigate against microvascular risks. Future trials in this area would be valuable.

South Asians – individuals of Pakistanis, Indians, Bangladeshis and Sri Lankans – represent almost a quarter of the world's population. Many South Asians live outside the Indian subcontinent with large populations in the UK (approximately 3 million people), Canada (1.6 million), South Africa (1.3 million), the USA (3 million), many European countries, the Middle-East, Australia and several African countries. This review concentrates on the accelerated type 2 diabetes risks in immigrant South Asian populations; however, many aspects are pertinent to understanding the accelerated diabetes risk in all South Asians.

Search strategy

We searched PubMed and Google Scholar using the terms 'South Asian*', 'Asian Indian*', and keywords: : 'diabetes', 'impaired glucose tolerance', 'insulin*', 'glucose', 'obesity', 'adipose tissue', 'ectopic fat', 'muscle', 'liver', 'lifestyle', 'fitness', 'physical activity', 'gene*', 'early origins', 'fetal programming', 'diet' and selected relevant papers published in English from January 1970 to June 2015. In places we used our judgement to select representative papers or reviews to illustrate key points and issues rather than provide an exhaustive list of all the available studies on a particular topic.

Epidemiology of type 2 diabetes in migrant South Asians

How high is diabetes risk in South Asians?

Immigrant South Asians generally have greater prevalence of type 2 diabetes than the background populations of countries they move to (1-5). Relative to white people of European descent, South Asians living in high-income countries have age-standardised rates of type 2 diabetes around 2-4 fold higher, with these risks appearing highest in Bangladeshis (around 4-fold) and lowest in Indians (around 2-fold) (2;6). Of particular note, increased risk for diabetes is observed at much lower levels of body mass index (BMI) in all migrant

South Asian groups (1;7), as recently demonstrated using UK Biobank data (Figure 1) (1). Consequently, the American Diabetes Association (ADA) recently recommended lowering the threshold for diabetes screening to BMI ≥23 $kg.m^{-2}$ in Asian Americans (8) and the UK National Institute for Health and Care Excellence (NICE) have recommended thresholds of 23 $kg.m^{-2}$ and 27.5 $kg.m^{-2}$ to identify South Asians at 'increased' and 'high' risk of type 2 diabetes (9). However, the ADA and NICE BMI thresholds are pragmatic and an alternative more holistic approach would be to capture the South Asians' excess risk by incorporating ethnicity as a risk multiplier in diabetes risk scores (6).

At what age does the higher risk of type 2 diabetes in South Asians become evident?

A recent report from the Born in Bradford study demonstrated ~10% higher umbilical cord insulin levels in South Asian, compared with white European neonates born in the UK despite lower birth weights (10), suggesting greater insulin resistance at birth, extending earlier findings in South Asian neonates born in India compared with white European babies in the UK (11). Furthermore, South Asians in the UK appear more insulin resistant than white Europeans throughout childhood, with observations of higher insulin and triglyceride concentrations at 8-11 years (12), and higher glucose, insulin and HOMA-estimated insulin resistance at 13-16 years (13)in the Ten Towns Heart Health Study; and higher HbA1c, fasting insulin and fasting triglyceride, and lower HDL-cholesterol concentrations in 9-10 year old, despite lower BMIs and waist circumferences, in the CHASE study (14). These findings concur with analmost 3-fold greater incidence of type 2 diabetes in UK South Asians compared with white Europeans aged under 30 years (15). Incidence of type 2 diabetes continues to be higher in South Asians throughout middle-age and into later life (16). South Asians are typically diagnosed with type 2 diabetes around 5-10 years earlier than white

Europeans (17-19) and, by the age of 70, 30-40% of British South Asians have type 2 diabetes – at least twice the prevalence in British white Europeans (16). Thus, metabolic dysfunction and type 2 diabetes is more common throughout the life-course in South Asians (Figure 2). There is also evidence that South Asians may transition through the high risk 'pre-diabetes' phase more rapidly than white Europeans. Data from high-income countries are lacking, but evidence from the CURES study in India (20), a prospective follow-up of South African Indians (21), and the control arms of diabetes prevention trials in India (22;23), suggest an annualised progression rate to diabetes of ~12-18% for South Asians with IGT, which is substantially higher than the progression rate observed in people with IGT of white European origin (~5-11%) (24-27). Thus early intervention for diabetes prevention may be particularly important in this ethnic group.

Mechanisms: current hypothesis for why South Asians are at increased risk of diabetes

Increased risk of type 2 diabetes in South Asians probably results from the interaction between a number of innate and environmental factors. Current hypotheses for the mechanisms responsible for South Asians' increased diabetes risk are described in the section below and summarised in Figure 3.

Do South Asians have increased genetic predisposition to diabetes?

In a recent meta-analysis of genetic data including 29,618 cases and 40,329 controls from 38 studies, Sohani and colleagues (28) noted 24 single nucleotide polymorphisms (SNPs) from 21 loci were associated with type 2 diabetes in South Asians, with no clear evidence of a difference between the two ethnic groups in either the type 2 diabetes risk estimates associated with these SNPs or in their population burden. There is, however, recent evidence from an epigenome-wide association study in 13535 South Asians and 7066 white Europeans

in the London Life Sciences Prospective Population (LOLIPOP) study that a DNA methylation score based on five genes – ABCG1, PHOSPHO1, SOCS3, SREBF1, and TXNIP – was similarly predictive of type 2 diabetes in white Europeans (relative risk of 1.88 per SD increase) and South Asians (relative risk of 1.68), but that South Asians had a DNA methylation score 0.86 SD higher than the Europeans. This 'explained' 32% of 2.5-fold increased diabetes risk in South Asians that was not accounted for by differences in adiposity, glycaemic measures or physical activity (19). Such findings require replication, particularly in children, to help reveal the extent to which this effect is seen early in life, when noise from cumulative exposure to environmental risk factors is lower than in adulthood (29).

Is there a role for early origins/fetal programming?

A recent meta-analysis showed low birth weight (a marker of fetal undernutrition) to be associated with greater risk of type 2 diabetes with each kg increase associated with a ~25% decrease in diabetes risk (30). Whilst South Asians have lower birth weights, a recent analysis from different ethnicities did not support low birth weight *per se* as an explanation for the emerging ethnic difference in risk markers for diabetes (31). However, South Asian children have a higher percentage of body fat at birth (based on skin-folds and/or cord leptin levels), often accompanied by higher cord insulin concentrations commensurate with greater insulin resistance (10;11). Of note, when adjustment was made for maternal fasting glucose levels, which were higher in the (predominantly Pakistani) South Asian women, the ethnic difference in cord leptin halved and became non-significant (10). Further analyses of 1,415 women and their singleton live-born infants (629 white British and 786 Pakistani) supported the hypothesis that maternal fasting glucose levels may mediate the relationship of Pakistani ethnicity to greater fat mass at birth (10). If correct, future randomised trials investigating the effects of lifestyle intervention in South Asian pregnant women at elevated risk of gestational diabetes would seem worthwhile, with key end-points including rates of gestational diabetes,

birth weights and, critically, neonatal body composition. Such intervention trials are important to translate the research into the fetal programming hypothesis beyond mere observations and elucidation of mechanisms to real-world clinical importance.

Do South Asians have lower pancreatic beta-cell capacity?

In contrast to clear evidence for greater insulin resistance in South Asians, there is less evidence for inadequate beta-cell capacity. However some recent data, using indirect measures, has emerged. Data from the Whitehall study in the UK (32), using HOMA-B% as an estimate of beta-cell function in 230 South Asian and 5749 white European participants aged 39-79 at baseline assessed at 5-yearly intervals from 1991-1994 to 2007-2009, suggest that beta-cell function is higher in South Asians at age 50 years, a finding corroborated by data from the Southall study (16); however, while HOMA-B% increased in Europeans with age to compensate for increasing insulin resistance, this did not occur in South Asians, who experienced a decline in beta cell function from the age of ~60 years onwards (32). Interestingly, cross-sectional data from the MASALA and MESA studies in the US showed slightly lower HOMA-B values in South Asians (mean age 57 years) compared with adults of white European descent (mean age 63 years) (33). Furthermore, in the Whitehall study, there was clear evidence of a sharper rise in fasting plasma glucose in South Asians compared with white Europeans over time (32). Interestingly, in the Southall study, whilst adjustment for truncal adiposity and insulin resistance completely attenuated the excess incident diabetes risk in South Asian women, the excess diabetes risk remained in South Asian men, suggesting inadequate compensatory beta cell function may contribute (16). One limitation of HOMA-B% is that it provides a relatively crude estimate of beta-cell function. In a study of migrant South Asians in the US, Gujral and coworkers found that the disposition index – a more dynamic estimate of beta cell function, derived from glucose and insulin

measures across an OGTT – was more strongly associated with 'pre-diabetes' and type 2 diabetes than whole body insulin sensitivity assessed using the Matsuda index. Clearly, further detailed assessment of beta cell function in South Asians across the life-course appears warranted. In general, whilst South Asians are able to produce more insulin at younger ages to compensate for their peripheral insulin resistance, it appears that an earlier decline in beta cell function accompanies transition to dysglycaemia and ultimately diabetes. Whether these patterns represent earlier beta cell 'exhaustion' secondary to higher levels of insulin production needed throughout the life-course to compensate for insulin resistance; lower inherent beta cell capacity; more rapid accumulation of ectopic fat around the pancreas; or some other mechanism such as enhanced hepatic insulin extraction, requires further investigation. The clinical implications of these findings are also uncertain, though some speculate that incretin-based therapies may be particularly suitable for South Asians with diabetes (34).

Do South Asians have a lower capacity for safe fat storage than Europeans?

In observational studies, the increase in diabetes risk per unit increase in BMI or waist circumference is substantially greater in South Asians than Europeans (1;7) suggesting that the adverse metabolic effects of increasing adiposity may be greater in South Asians. Indeed, while South Asians carry more body fat than Europeans and this is distributed more centrally (35-38), they remain more insulin resistant than Europeans after adjustment for a range of adiposity markers (38-40). However, these relatively crude adjustments do not account for potential differences in adipose tissue morphology or function. Whilst there is evidence that excess subcutaneous truncal fat is associated with insulin resistance (41), it has been postulated that accumulation of fat in primary superficial subcutaneous adipose tissue depots is relatively benign, whereas fat accumulation in secondary deep subcutaneous, visceral and

ectopic depots is associated with metabolic dysfunction (42-44) . Accordingly, it has been hypothesised that South Asians have a lower capacity to store fat in the primary superficial subcutaneous adipose tissue compartment than Europeans resulting in earlier 'overflow' into more harmful secondary depots – the adipose tissue overflow hypothesis (44;45). Indeed, the available data generally indicate that South Asians store a larger proportion of their total and/or abdominal fat in deep subcutaneous and visceral depots compared with Europeans (35;44-49). Nevertheless, such data are limited by their cross-sectional nature and further longitudinal or intervention trial data are needed to confirm whether South Asians do start to accumulate deep subcutaneous and visceral fat earlier than white Europeans as they increase adiposity, and whether this contributes to their increased susceptibility to diabetes.

Observations of adipose tissue distribution do not address underlying mechanisms responsible for the hypothesised reduced fat storage capacity in South Asians. Chandalia and colleagues reported that South Asian men have a larger mean subcutaneous abdominal adipocyte size than Europeans (35), and Anand co-workers reported that South Asians had greater subcutaneous abdominal adipocyte area and larger adipocyte maximum diameter than Europeans (45). However, recent evidence suggests that adipocyte size follows a bi-modal or tri-modal distribution, which is not adequately described by simply reporting mean adipocyte size (50-52). These studies suggest that insulin resistant obesity is characterised by an increased proportion of small adipose cells (50;51) and larger large adipose cells (50;52). This has been interpreted to reflect an inability for small adipose cells to terminally differentiate into mature adipose cells and increase triglyceride storage in insulin resistant individuals, which leads to increased size of the limited pool of large adipocytes and earlier storage in ectopic depots (50;51). Indeed, adipogenic gene expression in the insulin resistant obese appears reduced (50;53). Consistent with these reports, a recent study reported that

South Asians have both a higher ratio of small-to-larger adipocytes, and a larger fraction of very large adipocytes than Europeans (54). However, once again, such data are limited by their cross-sectional nature, and longitudinal and/or intervention data are needed to ascertain whether differences exist between South Asians and Europeans in adipocyte size changes with weight gain; the molecular mechanisms responsible; and whether these changes contribute to the observed ethnic differences in diabetes risk.

One consequence of the adipose tissue overflow hypothesis in South Asian would be accumulation of greater levels of liver fat at any given level of adiposity, which has been recently examined(45;55). One report observed higher liver fat only in South Asian men (55), whereas another found the ethnic difference in liver fat to be more pronounced in women (45). Interestingly, liver fat content remained ~2-fold higher in South Asian compared with European men after adjustment for insulin sensitivity in the former report (55), suggesting that the relationship between liver fat content and insulin sensitivity may not be identical across ethnic groups. Clearly, further studies are needed in this area, which should also include pancreatic fat measurements.

There has been recent interest in brown adipose tissue (BAT) which is a heat generating form of fat with positive effects on energy homeostasis (56;57), adiposity (58) and glucose metabolism (58;59). Two studies have investigated potential differences in BAT between South Asians and white Europeans with conflicting findings (60;61), thus further research is needed..

Is lower lean body mass / skeletal muscle mass implicated?

South Asians have proportionately less lean tissue than white Europeans for a given BMI. As skeletal muscle is the quantitatively the most important site of glucose disposal (62), it is conceivable that this could contribute to their greater insulin resistance and diabetes risk. Lear and colleagues reported that South Asian men and women (n=202) had higher body fat percentages, lower lean mass, a higher fat-to-lean mass ratio and were more insulin resistant than Europeans (n=208) (63). South Asians remained more insulin resistant than Europeans after adjustment for fat mass, but the ethnic difference in insulin resistance was no longer significant after adjustment for the fat-to-lean mass ratio, implying a contribution of lean tissue to South Asians' excess insulin resistance (63). Similarly, in a study of 514 South Asians and 669 Europeans aged 56-86 years, Eastwood and colleagues reported that South Asian men and women had lower thigh muscle cross-sectional areas, and that thigh muscle area was significantly negatively associated with HbA1c in South Asians (but not Europeans) in analyses adjusted for relevant confounders (47). Thigh muscle adjustment attenuated the excess diabetes risk observed in the South Asians independently of visceral adipose tissue (47). Thus, lower lean mass may contribute to the increased diabetes risk in South Asians but, from the available data, it is difficult to fully disentangle the potential independent effects of lower lean mass *vs* greater fat mass on metabolic profile and diabetes risk. Resistance exercise, which increases muscle mass, could conceivably become an important strategy (together with weight loss and increased aerobic physical activity) for diabetes prevention in South Asians and randomised controlled trials to determine the efficacy of this approach are needed.

Do lower levels of physical activity and fitness play a role?

Epidemiological studies show that low levels of physical activity are associated with increased risk of type 2 diabetes (64;65), independent of BMI (65), and data from diabetes prevention lifestyle intervention trials demonstrate the potential for increasing physical activity to reduce incidence of diabetes, which is evident even in trials in which there was not significant weight loss (22;66). A number of studies using both objective accelerometer (67-69) and self-report questionnaire (47;70-73) measures of physical activity have reported that South Asians living in high-income countries are less active than white Europeans throughout the life-course. However, although lower physical activity levels likely to contribute to their higher level of insulin resistance and diabetes risk , South Asians remain more insulin resistant than white Europeans after adjustment for difference in physical activity level (39;67).

A contributing factor may relate to differences between South Asians and Europeans in the association between physical activity and cardiorespiratory fitness. Physical activity is a behaviour, defined as bodily movements produced by skeletal muscles which results in energy expenditure, whereas cardiorespiratory fitness is the ability of the cardiovascular and respiratory systems to supply oxygen to working muscles during sustained physical activity. There is a relatively strong relationship between level of physical activity and level of cardiorespiratory fitness (74), however, increasing evidence suggests that South Asians have lower levels of cardiorespiratory fitness than white Europeans (39;74-76), which cannot be accounted for differences in physical activity (39;74). There is substantial epidemiological evidence that cardiorespiratory fitness level is an important risk factor for type 2 diabetes (77-83), and evidence from animal models supports the likely causality of this relationship (84). Indeed, adjusting for differences in fitness between South Asian and white European men attenuated the excess (HOMA-estimated) insulin resistance observed in the South Asians by

more than two-thirds (74) (Figure 4), although similar studies are needed in women. As increases in fitness can only be brought about by physical activity or losing weight (as maximal oxygen uptake is generally expressed per kg body weight), South Asians need to engage in greater levels of physical activity and/or have a lower body weight to achieve comparable levels of fitness (and insulin sensitivity) to white Europeans. In line with this, recent Indian physical activity guidelines (85) and the Joint British Societies' in the UK (86) have both recommended substantially higher levels of physical activity for South Asians for diabetes and cardiovascular disease (CVD) prevention, than the current WHO physical activity recommendation of 150 minutes of moderate intensity physical activity per week (87). Given that habitual levels of physical activity are currently lower in South Asians than Europeans in high-income countries (67-73), realising such a change will be a considerable but important challenge.

We have also reported that fat oxidation during sub-maximal exercise (which largely reflects muscle metabolism) was about 50% lower in South Asian men compared with age and BMI-matched white European men, and that this was associated with lower insulin sensitivity at both the whole body level and the level of insulin signalling within skeletal muscle (39). However, paradoxically, despite lower cardiorespiratory fitness and fat oxidation during exercise, South Asians did not have lower skeletal muscle expression of oxidative and lipid metabolism genes, and the skeletal muscle mitochondrial to nuclear DNA ratio was similar between the two ethnic groups, suggesting similar mitochondrial biogenesis (39). Bakker and colleagues recently reported that, compared to European men of similar age and BMI, young normoglycemic South Asian men had a lower mitochondrial to nuclear DNA ratio, but similar expression of oxidative, lipid and glucose metabolism genes in skeletal muscle (88). In contrast, data from Nair and co-workers suggest that skeletal muscle capacity for oxidative

phosphorylation and mitochondrial DNA copy number may be higher, rather than lower, in South Asians compared with white Europeans (89). Thus, based on the limited available data, skeletal muscle mitochondrial dysfunction appears unlikely to account for South Asians increased insulin resistance although further studies are needed. There is increasing evidence that a substantial component of 'muscle' insulin resistance may reflect insulin resistance of the muscle vasculature (90), and impaired endothelial function in forearm resistance vessels (91) and reduced bioavailability of nitric oxide at rest and during exercise (92) has been observed in young South Asian compared with white European men. Thus, impaired skeletal muscle microvascular function may contribute to increased insulin resistance in South Asians but further study is needed to quantify the magnitude of any such effect.

Can a poorer diet explain the excess diabetes risk in migrant South Asians?

There is some evidence that dietary acculturation occurs in migrant South Asians such that, over time, eating habits become closer to those of the background population in their adopted country with increased consumption of highly processed foods and meat, and consequently higher energy and fat intake compared with diets traditionally consumed in South Asia (93;94). Nevertheless, reports have suggested energy intakes are similar or lower in migrant South Asians compared with white Europeans, with mixed reports on differences in dietary macronutrient composition (95-97). However, a report from the CHASE study suggested that South Asian children, particularly those of Bangaldeshi origin, aged 9-10 had higher energy, fat and protein intakes than white Europeans (98). Thus, overall, while South Asians' diets do appear to change when they migrate to high-income countries, there is no consistent evidence that their diets are any 'poorer' than the diets of the background populations of their adopted countries. However, the adverse metabolic effects of a high-fat, high energy diet (or over-consumption) may be greater in South Asians than Europeans. In a study of 12 young

lean South Asian (age 19-25 years, BMI <25 kg.m^2) and 12 age and BMI-matched European men in the Netherlands, overfeeding with 1275 kcal/day (94% fat) for 5 days significantly increased fasting glucose and insulin (by 48%) concentrations, and reduced insulin sensitivity (by 20%) in the South Asian but not the European men (88). Longer term overfeeding studies would be useful to extend such findings.

Prevention of type 2 diabetes in South Asians

There have been relatively few lifestyle intervention trials for the prevention of diabetes in migrant South Asian populations. Recently, the PODOSA trial, reported non-significant 28.4% reduction in progression to diabetes in the lifestyle intervention compared to control in South Asians with IFG and/or IGT in Scotland (99), although this trial was powered to address weight loss, rather than incident diabetes. Nevertheless, this percentage reduction in diabetes incidence was similar to that observed in the Indian Diabetes Prevention Programme 1, which demonstrated that lifestyle intervention (increased physical activity and healthy diet advice), metformin, and combined lifestyle and metformin, all induced similar reductions in diabetes incidence (26-28%) in South Asians with IGT in India (22). More recently, a trial of 537 patients with IGT in India randomised to a lifestyle modification intervention delivered by mobile-phone text messages or control, reported a 34% reduction in diabetes incidence with intervention (23). Thus, while there is evidence that lifestyle interventions to can reduce diabetes incidence in South Asians living in India, further trials are needed to demonstrate effectiveness of such interventions in high-income countries. It is of note that the percentage reduction in diabetes incidence with lifestyle intervention in trials in South Asians (28-34%) appear somewhat lower than that observed in other large diabetes prevention trials (e.g. 58% reduction in both the DPP and DPS (26;27)), suggesting a more modest effect of the lifestyle intervention employed to date in reducing diabetes risk in South Asians with 'pre-diabetes'.

The corollary of this is that earlier and/or more intensive intervention in South Asians may be needed to maximise the potential for lifestyle intervention to prevent diabetes in this ethnic group (Figure 2). In particular, given the evidence of more rapid acceleration of glycaemia levels (particularly fasting glucose) throughout adulthood in migrant South Asians, compared with white Europeans, (32), together with evidence that South Asians living in India experience a more rapid transition through the 'pre-diabetic' stage (20-23), an extension of the HbA1c range to categorise 'high diabetes risk' or pre-diabetes from 6.0-6.4% (100) to 5.7-6.4% in South Asians, to trigger earlier intervention, may be advantageous. Alternatively, glycaemia testing could be repeated at shorter periods (e.g. 6 months) in South Asians at elevated diabetes risk (from questionnaire-based screening), rather than the currently recommended 12-month interval. Randomised controlled trials to test the effectiveness of earlier intervention, more frequent screening and more intensive intervention (which may include a muscle strengthening component, as well as weight loss and increased aerobic physical activity) are urgently needed to address this.

Migrant South Asians with type 2 diabetes – clinical considerations

There is evidence that migrant South Asians with type 2 diabetes experience more rapid year-on-year deterioration in HbA1c than white Europeans in routine clinical practice, despite greater prescription of oral glycaemic agents (101), implying an ethnic difference diabetes progression rates. This section examines relative risks in South Asians with type 2 diabetes living in high-income countries for macro- and micro-vascular complications, and mortality, and will consider which outcome risks may have declined over time, which require more study, and which risk factors need further assessment in terms of timing, intensity and goals. A recent helpful review has called for ethnic specific guidelines for the prevention, diagnosis, and management of type 2 diabetes in South Asians living on the Indian sub-continent (102).

Whilst several aspects overlap, particular clinical issues relevant to migrant South Asian populations are highlighted here.

Macrovascular complications

Type 2 diabetes *per se* increases risk of cardiovascular disease (CVD) by around two-fold (103), and thus the higher CVD risk in South Asians in general must be accounted for, at least in part, by their greater diabetes prevalence. What is less clear is whether type 2 diabetes is more strongly linked to CVD in South Asians than white Europeans. Evidence from studies where type 2 diabetes developed around three decades ago does suggest a greater increase in CVD risk with diabetes in South Asians, particularly for stroke, in keeping with evidence that type 2 diabetes development at younger ages is associated with a greater relative increase in CVD risk than later development (104). That noted, risks appear to have attenuated over time. For example, in the Southall studycohort recruited around 1988 and 1991, type 2 diabetes was around twice as strongly related to stroke risk in South Asians and slightly more strongly related to CHD risk than in white Europeans (105;106). In the UKADS study, where type 2 diabetes developed around mid-1990s, South Asians had an adjusted odds ratio of 1.4 (0.9 to 2.2) for CVD events compared with white Europeans (107). A more recent report from Scotland in which diabetes was diagnosed on average around 2003 noted that excess CVD risk was apparent only in Pakistanis (HR 1.45) but not Indians (108). In this latter study, Pakistanis had poorer glycaemia and developed diabetes earlier than did Indians, in keeping with their higher risks. Finally, in a large population cohort from Canada which examined CVD risks over time in newly diagnosed type 2 diabetes patients between 2002 to 2009, hazard ratios for CHD were similar in South Asians and Europeans, and though this study did not adjust for some important risk factors such as smoking and obesity, overall mortality risks were also less (109). Overall, it appears that CVD risks associated with type 2

452 diabetes in migrant South Asians may have declined over time. This pattern would be
453 consistent with improvement in risk factor management in South Asians with type 2 diabetes,
454 particularly in lipids and blood pressure (particularly important to lowering CVD risk in
455 diabetes (110)), and potentially earlier pick-up of diabetes commensurate with greater
456 glycaemia testing in general. Furthermore, as South Asians develop T2DM at a younger age,
457 and as recommendations to treat all adult type 2 diabetes patients (>40 years of age) with
458 statin gained wider acceptance, south Asians may have gained greater relative CVD benefit
459 (thus attenuating their higher risk) by having an earlier and therefore longer exposure to
460 statins than white Europeans with type 2 diabetes. The same observation may also apply to
461 earlier exposure to anti-hypertensive use in South Asians with diabetes, though there appears
462 room for further improvement in uptake of anti-hypertensive therapy to mitigate
463 microvascular risks which remain high (discussed below). Future trials assessing benefit to
464 risk ratios of ethnic-specific treatment targets in blood pressure would be useful.
465
466 *Total mortality risks*
467 This is an area less well studied but interestingly, contemporary data from the UK National
468 Diabetes Audit reported lower short term mortality risks in South Asians with type 2 diabetes
469 relative to comparable white Europeans (111), in line with emerging evidence discussed
470 above from Canada (107). Whether these observations reflects lower non-cardiac death rates
471 or are, to some extent, influenced by earlier age of diagnosis and thus earlier exposure to
472 CVD preventative therapies in South Asians merits further study.
473
474 *Microvascular complications*
475 South Asians with type 2 diabetes appear to have a greater prevalence of retinopathy than
476 white Europeans. In the UK Asians Diabetes Study, conducted around 7-10 years post-

diagnosis, age and sex-standardised retinopathy prevalence was significantly higher in South Asians than white Europeans (43.3% *vs* 37.2%), with a borderline difference in maculopathy (14.4% *vs* 8.8%) (112). Similarly, in a South African-based study, Thomas and colleagues reported ~2-fold higher rates for both retinopathy and referable retinopathy in South Asians compared with white Europeans, assessed about 5 years post-diagnosis (113) . Interestingly, in the South London Diabetes (SOUL-D) cohort, in which patients were recruited within 6 months of diagnosis, prevalence of retinopathy in South Asians and white Europeans was similar (17.0% vs 16.6%), although South Asians were on average 7 years younger and had lower systolic blood pressure (114). HbA1c concentrations were higher in the South Asians compared with Europeans in each of these reports (112-114), in keeping with their greater retinopathy risks. As this higher glycemia was already evident at or early after diagnosis (114), delayed diagnosis, or lesser response to early diabetes treatment or more rapid progression may contribute.

The available evidence suggests that microalbuminuria prevalence is similar or lower in South Asians compared with white Europeans early after diagnosis of type 2 diabetes (114), but about 1.4-2 fold higher 9-20 years post-diagnosis (17;115). In a longitudinal study in the Netherlands, South Asian diabetes patients without microalbuminuria at baseline had 4-fold higher odds for development of micro- or macroalbuminuria compared with white European patients, and a 1.45-fold greater decline in glomerular filtration rate (GFR) (116). This latter finding was recently corroborated in a multi-ethnic community cohort with diabetes in London, where the annual decline in GFR was 44% greater in South Asians (117). Taken together, these findings suggest more rapid progression towards nephropathy in South Asians with diabetes. Interestingly, in these two longitudinal reports, HbA1c levels were 0.4-0.8% higher in South Asians than Europeans, but South Asians had lower systolic blood pressure,

and similar or lower use of antihypertensive drugs (116;117). In particular, antihypertensive use may be lower in South Asians in the early stages of diabetes (114) – perhaps due to their lower blood pressure and younger age at diagnosis – but catches up with disease progression as microalbuminuria rates rise more rapidly (117). Given the above, it is unsurprising that South Asians have higher risks of developing end-stage renal disease (118). They do, however, seem to do well on dialysis with better survival rates than white Europeans, although, as well documented, they suffer from far lower rates of renal transplantation due to lack of donors (119).

Paradoxical to the elevated risks of other microvascular complications, South Asians have lower neuropathy rates at diagnosis (114) and far lower rates of lower extremity amputations (120), linked in turn to lower rates of peripheral vascular disease. Previous work has suggested lower rates of smoking may contribute to this pattern of risk (120), though further studies would be useful.

Implications for clinical care

The foregoing information highlights the need for trials addressing ethnic-specific treatment targets in migrant South Asians. For example, consideration of early use of ACE/ARB in South Asians at the point of type 2 diabetes diagnosis may be helpful. At present, and as discussed above, South Asians with diabetes seem to have lower antihypertensive use early in the course of their disease. Nevertheless, their faster progression of retinopathy and nephropathy suggests they may benefit from earlier use of these medications. In light of recent meta-analysis data indicating additional benefits on retinopathy, nephropathy and stroke from achieving a blood pressure target of <130/80 compared to <140/90 (121), a trial testing a lower blood pressure threshold (<130/80) in younger South Asians with type 2

diabetes, with primary end-points of progression of retinopathy and nephropathy, but also considering safety and quality of life, would be valuable.

Perhaps most critically, more aggressive management of hyperglycaemia in South Asians early after type 2 diabetes diagnosis should be considered. This should include recommending more aggressive lifestyle changes and, where necessary, earlier increments in oral hypoglycaemia therapies (OHA). Whether there is a place for dual OHA therapy at diagnosis in some South Asians requires further study and could be trialled. There is also a need to do head to head comparisons of differing OHAs in South Asians to identify which second line therapies work best and whether different subgroups (by sex, age, adiposity levels) respond differently. Some observations suggest beta cell function may be a more important risk factor in transition from normoglycaemia to diabetes in South Asians, whereas other evidence implicates greater insulin resistance. It is therefore difficult to predict which drugs may work best, but given the rapidly rising prevalence of South Asians with type 2 diabetes, this is an area for urgent study. It would be useful for a study similar to the GRADE study (122), recently commenced in the US to compare the effectiveness of commonly used diabetes medications in combination with metformin on glycaemia and patient centred outcomes, to be repeated in a South Asian population.

Conclusions and Future Directions

We have reviewed the causes and consequences of higher type 2 diabetes risk in South Asians, concentrating predominantly on research from high-income countries, and thus from studies in migrant South Asians. Nevertheless, many aspects have relevance to South Asians in low and middle income countries where the rise in prevalence of the disease is extremely worrying. Based on our assimilation of the evidence, we have suggested a number of areas

for future mechanistic research, areas for public health consideration and future clinical trials in South Asian with and without type 2diabetes (summarised in Table 1). It is clear that many areas require further research investment but in advance of these, the major route to prevent diabetes in South Asians would be to reverse trends of rising obesity levels since South Asians appear more sensitive to rising obesity linked in part to differences in body composition (more fat, with a higher proportion of deep subcutaneous and visceral fat, and less muscle). Reversing obesity trends in general is no simple task and requires actions on a number of levels including governmental efforts and changes in food policy and travel infrastructures. Nevertheless, in advance of any such efforts, it is clear that South Asians need to be encouraged and helped (via multiple, culturally efficient methods) to maintain high physical activity levels and lower body weights throughout the life-course to prevent diabetes. In clinical terms, cardiovascular risks may have attenuated over time in South Asians with type 2 diabetes due to better blood pressure and lipid management but retinopathy and renal complication risks remain higher due to more rapid glycaemic deterioration over time. Thus greater efforts on improving glycaemic control in South Asians with diabetes are needed. Again we have suggested a number of potential means to address this. Further collaborative efforts between researchers in high and low and middle income countries with substantial South Asian populations should help improve our evidence base in this important area.

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Contributions:

Both authors conceived idea and scope for this review, conducted searches and wrote the manuscript and revised it prior to publication.

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Table 1. What is known, and future research directions for mechanisms, mitigation and management of type 2 diabetes in migrant South Asians. References for the points in the table made can be found in the main text of the paper. South Asian abbreviated to SA.

		What is known	Future research directions
Mechanisms	Adiposity	SA develop diabetes at much lower BMI than white Europeans. For a given BMI, SA have higher fat mass and a larger proportion of fat mass in deep abdominal subcutaneous and/or visceral depots. Emerging evidence for greater liver fat.	Detailed examination of ectopic fat depots to include more data on liver fat and pancreatic fat as determinants of hepatic insulin resistance and pancreatic beta cell function, respectively. Detailed examination of SA adipose tissue phenotypic features across life-course and with intentional weight loss and weight gain.
	Lean body mass	SA have a lower proportion of lean mass which appear to contribute to their higher insulin resistance and diabetes risk.	Interventions on the effects of resistance exercise to increase lean body mass on insulin resistance and diabetes risk in SA.
	Fitness and skeletal muscle function	SA have lower cardiorespiratory fitness (independent of physical activity level) and lower fat rates of fat oxidation during submaximal exercise. Both appear to contribute to their higher insulin resistance. However, from the available evidence it appears that skeletal muscle mitochondrial dysfunction is unlikely to account this.	Interventions using higher intensity exercise to maximise potential increases in fitness on insulin resistance and diabetes risk in SA. Studies to investigate whether impaired skeletal muscle microvascular function contributes to increased insulin resistance.
	Lifestyle	SAhave lower levels of physical activity than white Europeans.	Development of novel, culturally appropriate approaches to increase physical activity across the life-course in SA. This is particularly important for SA girls where activity levels fall off rapidly by secondary school age.
		No clear evidence for diet as major contributor to excess type 2 diabetes risk in migrant SA, but emerging data that SA may have greater adverse effects of short-term overfeeding.	Longer-term intervention trials needed on effects of specific dietary manipulations (dietary patterns/energy intake changes) on metabolic function/type 2 diabetes risk in SA needed. This area is relatively sparsely studied.
	Programming	Limited evidence for programming role in explaining greater SA type 2 diabetes risk. Lower birth weight *per se* does not explain higher risks. Preliminary evidence	Lifestyle intervention in pregnant SA women to determine if by lowering maternal glucose rise is achievable and, if so, whether this alters neonate body composition and future offspring metabolic risk

		that greater maternal hyperglycaemia in SA may contribute to greater fat mass in offspring.	profile.
	Beta cell function	Indirect evidence that beta cell function is higher in SA until middle age, but of earlier beta cell decline with rising age in SA.	More direct measurements of beta cell function (for example using FSIVGTT)
	Genetics /epigenetics	No current evidence for major differences in genetic risk factors for type 2 diabetes between SA and Europeans. Some recent evidence for epigenetic signals potentially relevant to excess diabetes risk in SA.	Continued research for type 2 diabetes genes across different ethnicities. Replication of epigenetic findings, particularly in children who have less cumulative environmental exposure. Whether there is any clinical applicability of the epigenetic findings in terms of risk prediction needs further investigation. This is currently unclear.
Mitigation	Prevention	Evidence for modest type 2 diabetes risk reduction via conventional and via mobile phone-facilitated lifestyle intervention, and for modest weight reduction with family based interventions in SA with impaired glucose tolerance. Addition of metformin or pioglitazone to lifestyle provided no additional benefit.	Trials of more intensive lifestyle interventions (greater amounts of physical activity, larger weight loss, and addition of resistance exercise) and/or earlier intervention (see below on widening 'high risk for diabetes' range).
	Public health measures	In line with above, preliminary evidence that SA need to undergo more physical activity and achieve lower BMIs to mitigate metabolic risks. This is starting to be reflected in public health obesity guidance, but not yet in physical activity guidance.	More research needed to determine appropriate levels of physical activity to minimise diabetes risk in SA to inform public health guidelines. In addition, research needed on which public health measures could cost-effectively lower diabetes risk in SA both in developed and developing countries (e.g. sugary drinks tax, culturally tailored education programmes, engagement of community leaders and media stars as advocates). Approaches taken are likely to be culturally specific and may differ country by country.
Management	Screening for type 2 diabetes or high diabetes risk	SA are known to develop diabetes at younger ages and lower BMI than white Europeans and screening strategies are appropriately adopted in some countries to reflect this.	All high-income countries with sizeable SA populations should develop risk scores for type 2 diabetes which are easy to use and include risk multipliers for their major ethnicities (e.g. QDIABETES in UK)

Widening 'high risk for diabetes" or "pre-diabetes" range	SA with impaired glucose tolerance or other risk factors appear to more rapidly convert to type 2 diabetes compared to Europeans, so that less time spent in intermediate hyperglycaemia categories.	A wider 'high risk for diabetes' or pre-diabetes window for SA (i.e. HbA1c 5.7 to 6.4% rather than 6.0 to 6.4%) may improve preventative efforts by increasing scope for implementation of earlier intensive lifestyle intervention
Lipids	CVD risks in SA with type 2 diabetes appear higher than in comparable white Europeans and thus mechanisms to lessen risks needed. Statins appear to be at least equally effective at lowering cholesterol levels in SA and average cholesterol levels in SA and Europeans with diabetes appear similar.	Whether all SA with type 2 diabetes above age of 35 years should be offered statins (rather than general threshold of 40 years recommended in most guidelines) would be usefully examined.
Blood pressure	Blood pressure values are broadly similar in SA and white Europeans with type 2 diabetes but anti-hypertensive use appears lower in SA in the early stages of disease, perhaps due to younger age at diagnosis and lower levels of obesity leading to lower perceived risk.	Whether early adoption of ACE /ARB in SA at the point of diagnosis with type 2 diabetes and lower blood pressure targets than in general (<130/80 mm Hg vs. <140/90 mm Hg) would help to attenuate excess microvascular risks needs investigation. Formal trials would be useful.
Glycaemia	Clear evidence of higher HbA1c at different stages of disease (including at diagnosis) in SA with type 2 diabetes and more rapid progression to treatment with insulin. Higher rates of retinal and renal disease in line with the foregoing.	More research is needed on how to lessen glycaemia levels in SA with type 2 diabetes. Specific examples include: the potential role of dual therapy at diagnosis in select groups; and more frequent visits to monitor HbA1c and progress in early years after diagnosis. The efficacy and side effect profiles of different second line therapies in SA should be examined in the same way such approaches being examined in US (GRADE study). More research needed on how to improve compliance with diabetes medications and to stimulate /facilitate better adoption of lifestyle changes.

Figure Legends

Figure 1. Age-adjusted associations between diabetes prevalence and adiposity in the UK Biobank study. This figure presents the relationship between diabetes prevalence and BMI in white European (black line), Pakistani (red line) and Indian (green line) women (left panel) and men (right panel). The horizontal maroon line shows diabetes prevalence for white Europeans with BMI 30 $kg.m^{-2}$, and dotted vertical lines indicate BMI values in each ethnic group providing the same diabetes prevalence to that observed in white Europeans with BMI 30 $kg.m^{-2}$. Modified from reference (1). Copyright 2014 by the American Diabetes Association.

Figure 2. Glycaemia over the life-course and the effect of lifestyle intervention on diabetes progression in South Asians and white Europeans. South Asians develop diabetes about 5-10 years earlier than Europeans and have more rapid progression from impaired glucose tolerance (IGT) to frank diabetes. Current lifestyle interventions in patients with IGT reduce diabetes progression by >50% in Europeans and ~30% in South Asians. Thus, to minimise diabetes risk in South Asians earlier and/or more intensive lifestyle intervention may be required.

Figure 3. Currently hypothesised mechanisms for South Asians' increased type 2 diabetes risk. A combination of innate and environmental factors interact to accelerate diabetes risk in South Asians via the potential mechanisms outlined. Colour intensity of boxes indicates the amount of supporting evidence for each factor, with a white background denoting the least supporting evidence, and a black background denoting the greatest amount of supporting evidence.

Figure 4. Relationship between homeostasis model-estimated insulin resistance ($HOMA_{IR}$) and maximal oxygen uptake (VO_{2max}) in South Asian (solid circles, solid line) and European (open circles, dotted line) men. $HOMA_{IR}$ values displayed as natural logarithms. Solid and dotted vertical bars indicate mean VO_{2max} values in South Asian and European men, respectively; the horizontal arrow shows the mean difference in VO_{2max} between ethnic groups. Solid and dotted horizontal bars, with corresponding vertical arrows indicate mean $HOMA_{IR}$ values in South Asian and European men and the mean ethnic difference, both unadjusted and adjusted for VO_{2max}. Adjustment for VO_{2max} attenuated the ethnic difference in $HOMA_{IR}$ by 67.5%. From reference (74).

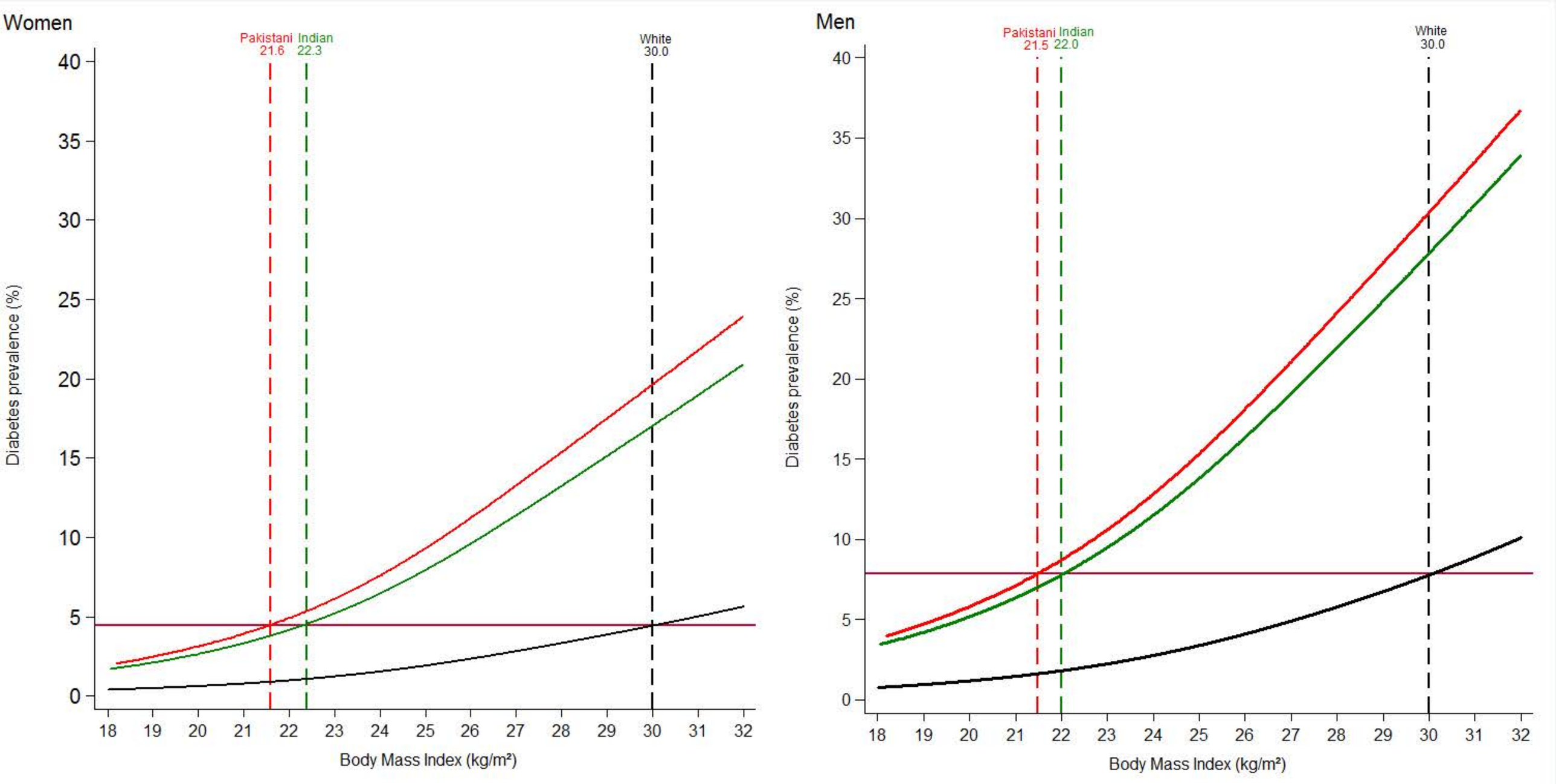

Women
Pakistani
21.6
Indian
22.3
White
30.0
Diabetes prevalence (%)
0
5
10
15
20
25
30
35
40
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
Body Mass Index (kg/m²)
Men
Pakistani
21.5
Indian
22.0
White
30.0
Diabetes prevalence (%)
Body Mass Index (kg/m²)

Figure 2

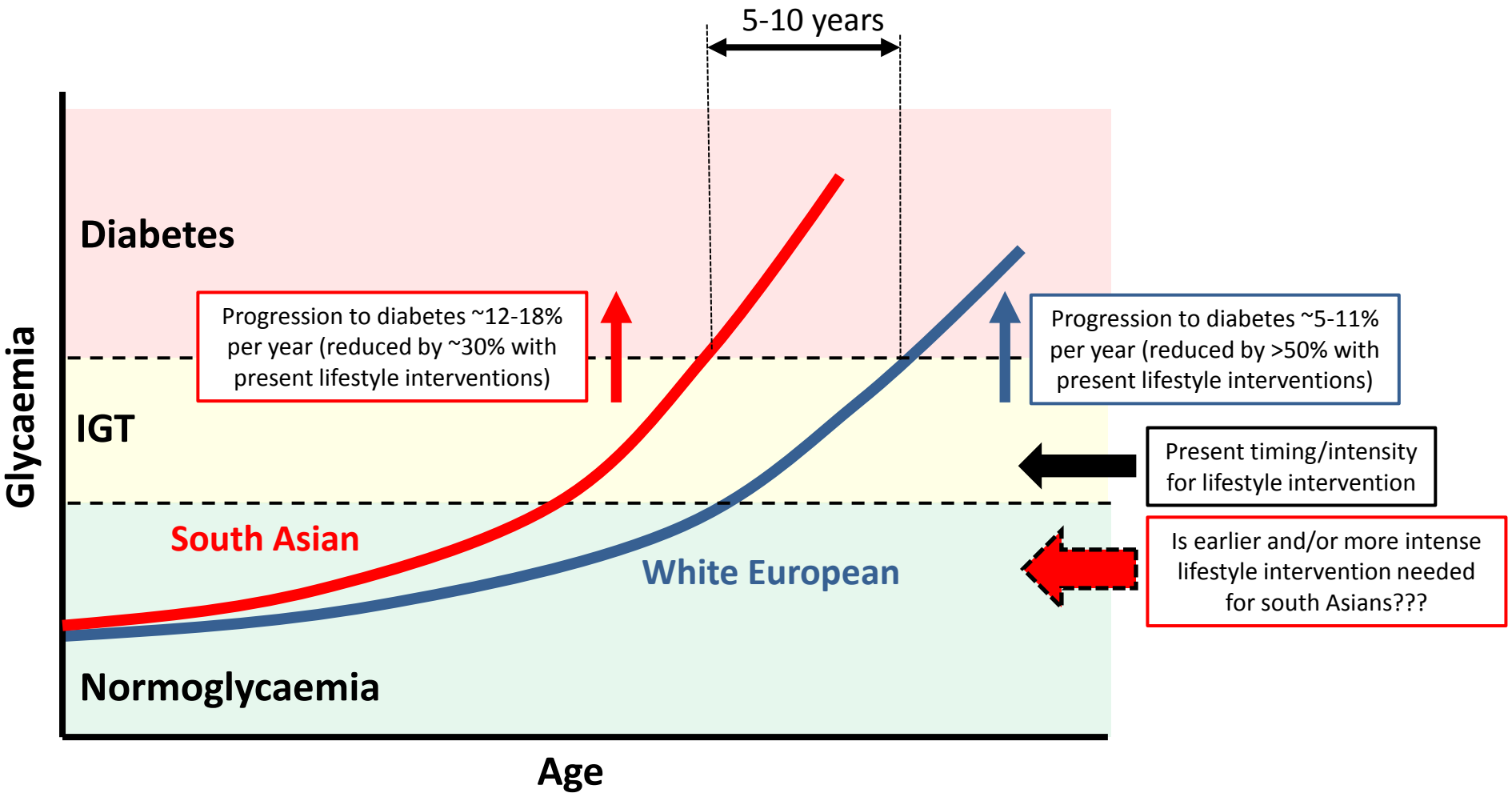

5-10 years
Diabetes
IGT
Normoglycaemia
Glycaemia
Age
Progression to diabetes ~12-18% per year (reduced by ~30% with present lifestyle interventions)
Progression to diabetes ~5-11% per year (reduced by >50% with present lifestyle interventions)
Present timing/intensity for lifestyle intervention
Is earlier and/or more intense lifestyle intervention needed for south Asians???
South Asian
White European

Figure 3

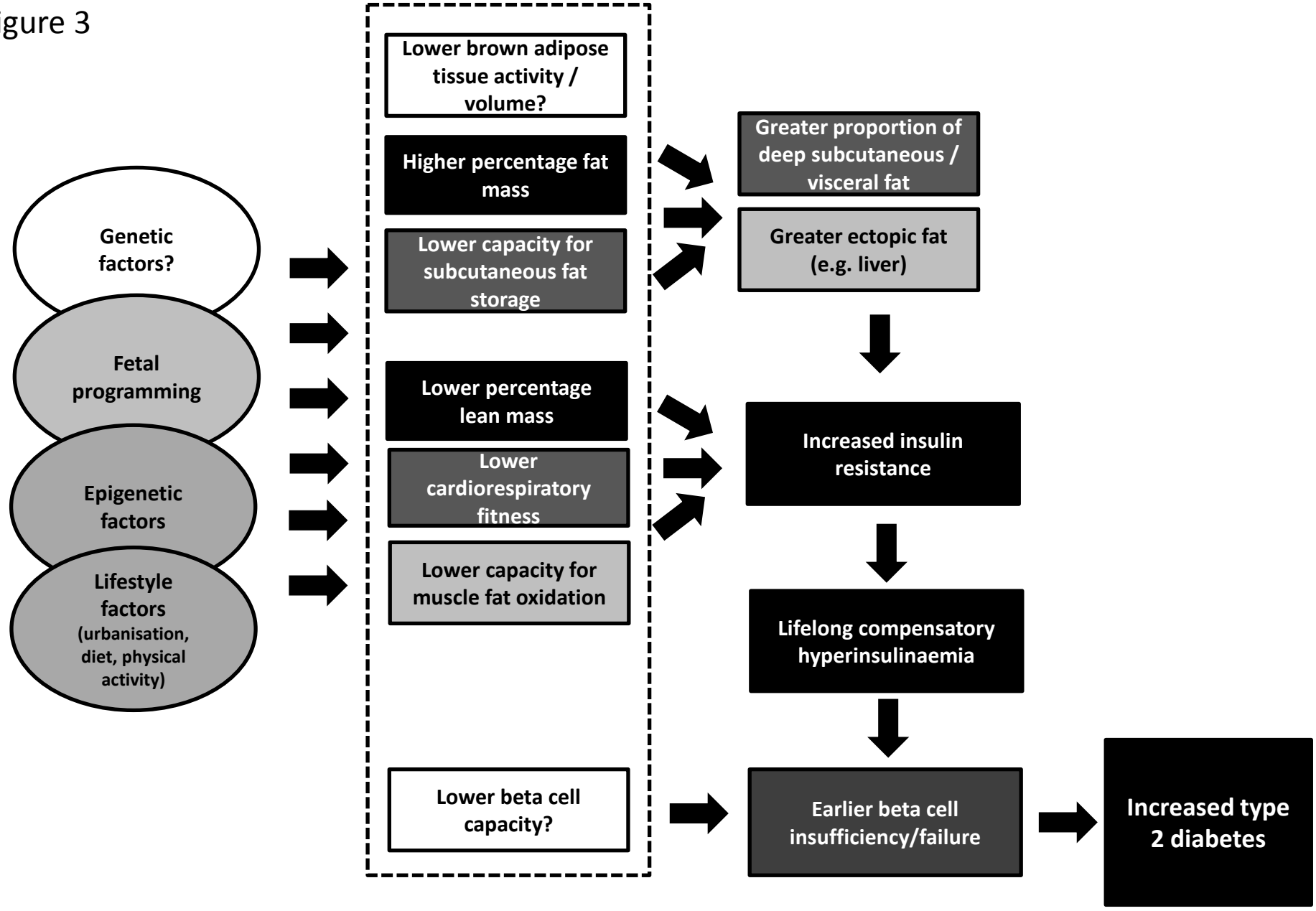
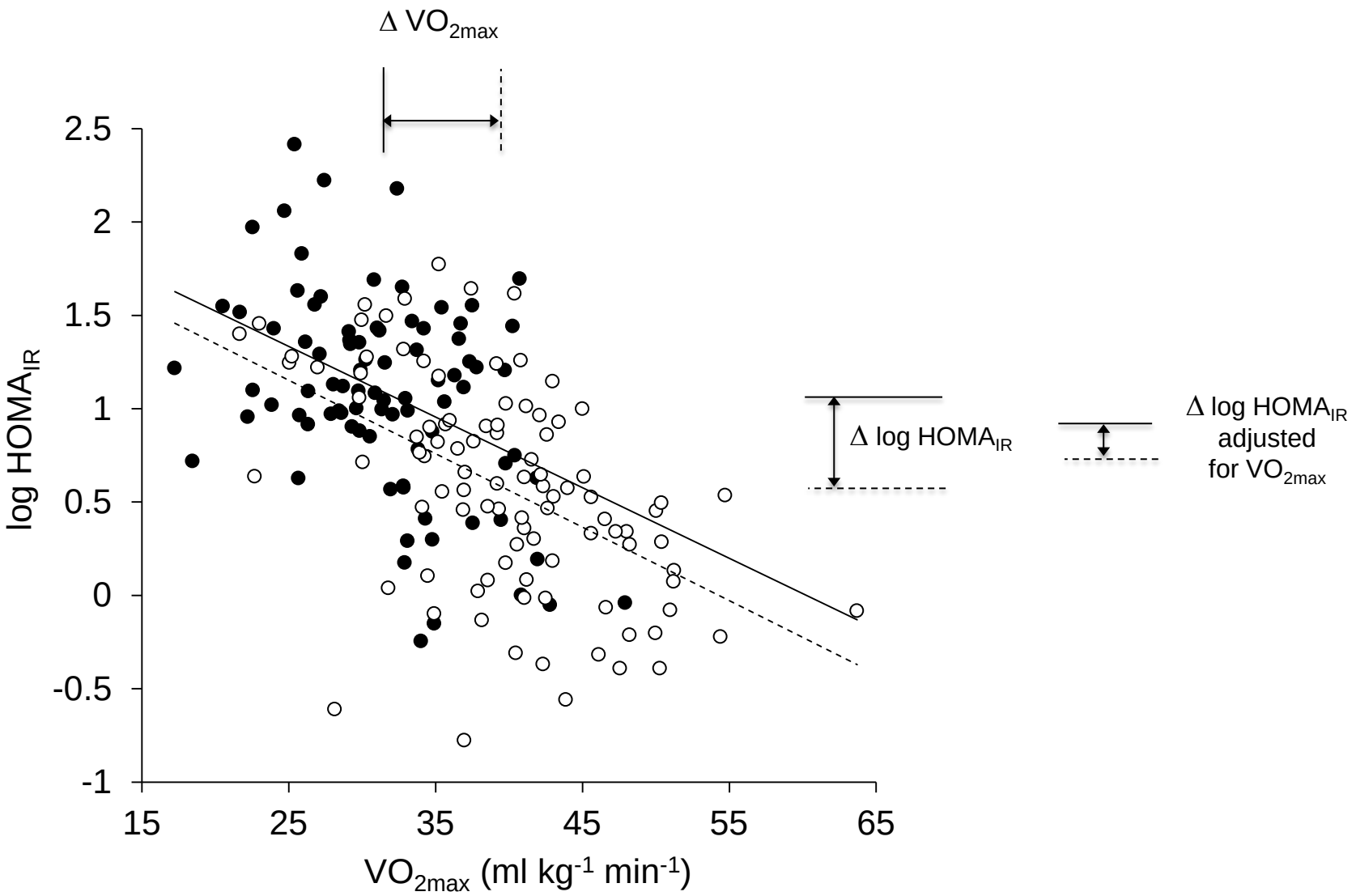

Genetic factors?
Fetal programming
Epigenetic factors
Lifestyle factors (urbanisation, diet, physical activity)
Lower brown adipose tissue activity / volume?
Higher percentage fat mass
Lower capacity for subcutaneous fat storage
Lower percentage lean mass
Lower cardiorespiratory fitness
Lower capacity for muscle fat oxidation
Lower beta cell capacity?
Greater proportion of deep subcutaneous / visceral fat
Greater ectopic fat (e.g. liver)
Increased insulin resistance
Lifelong compensatory hyperinsulinaemia
Earlier beta cell insufficiency/failure
Increased type 2 diabetes

Figure 4


Δ VO2max
2.5
2
1.5
1
0.5
0
-0.5
-1
log HOMAIR
15
25
35
45
55
65
VO2max (ml kg-1 min-1)
Δ log HOMAIR
Δ log HOMAIR adjusted for VO2max