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Title page

Effects of dietary and physical activity interventions on the risk of type 2 diabetes in South Asians: individual participant data meta-analysis of randomised controlled trials

Running title: Effects of Diabetes Prevention Interventions in South Asians

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Suggested tweet:

Lifestyle modification intervention trials in high-risk South Asian populations resulted in a 35% reduction in diabetes incidence. This metaanalysis shows that such interventions can reduce diabetes in these populations. #type2diabetes @Eurodhyan @UniOslo

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ABSTRACT

Background Individuals of South Asian origin have a high risk of type 2 diabetes (diabetes) and of deaths attributable to diabetes. Lifestyle modification intervention trials to prevent type 2 diabetes in high-risk South Asian adults have suggested more modest effects than in European origin populations. The strength of the evidence of individual studies is limited, however.

Aim We performed an individual participant data meta-analysis of available randomised controlled trials (RCTs) to assess the effectiveness of lifestyle modification in South Asian populations worldwide.

Methods We searched PubMed, Embase, Cochrane Library and Web of Science (to September 24th 2018) for randomised controlled trials on lifestyle modification interventions incorporating diet and/or physical activity in South Asian adults. Reviewers identified eligible studies and assessed the quality of the evidence. We obtained individual participant data on 1816 participants from all six eligible trials (four from Europe and two from India). We generated hazard ratio estimates for incident diabetes (primary outcome) and mean differences for fasting glucose, 2-hour glucose, weight, and waist circumference (secondary outcomes), using mixed effect meta-analysis overall, and by pre-specified subgroups. We used GRADE to rate the quality of evidence of the estimates. The study is registered as PROSPERO: CRD42017078003

Results Incident diabetes was observed in 12.6% of participants in the intervention groups and in 20.0% of participants in the control groups. The pooled hazard ratio for diabetes incidence was 0.65 (95% CI 0.51 to 0.81; I^2=0%) in intervention compared with control groups. The absolute risk reduction was 7.4% (95% CI 4.0-10.2), with no interactions for the pre-specified subgroups (sex, BMI, age, study duration, and region where studies were performed). The quality of evidence was rated as moderate. Mean difference for lifestyle modification versus control groups for 2-hour glucose was -0.34 mmol/l (95% CI -0.62 to -0.07; I^2=51%); for weight -0.75 kg (95% CI -1.34 to -0.17; I^2=72%) and for waist -1.16 cm (95% CI -2.16 to -0.16; I^2=74%). No effect was found for fasting glucose. Findings were similar across subgroups, except for weight for European versus Indian studies (-1.10 kg versus -0.08 kg, p=0.02 for interaction).

Conclusions/interpretation Despite modest changes for adiposity, lifestyle modification interventions in high-risk South Asian populations resulted in a clinically important 35% relative reduction in diabetes incidence, consistent across subgroups. If implemented on a large scale, lifestyle modification interventions in high-risk South Asian populations in Europe will reduce the incidence of diabetes in these populations.

Key words: Individual participant data meta-analysis, diet, physical activity, lifestyle intervention, prevention, randomised controlled trials, type 2 diabetes, South Asians

Abbreviations

GRADE Grading of Recommendations Assessment, Development and Evaluation

NNT Number needed to treat

PROSPERO Prospective register of systematic reviews

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Research in context summary

What is already known on this subject?

- Individuals of South Asian origin have a substantially higher risk of type 2 diabetes (diabetes) and a higher proportion of deaths attributable to diabetes than individuals of European origin.
- Lifestyle modification has been found to be effective in preventing diabetes in European-origin populations.
- Diabetes prevention trials among South Asian adults seem to be less effective than in other populations.

What is the key question?

- Do lifestyle modification interventions prevent diabetes in South Asian adults?

What are the new findings?

- This systematic review and individual participant data meta-analysis changes our thinking on the assumed limited effect of lifestyle modification interventions in high-risk South Asian individuals; we found evidence of a meaningful 35% relative reduction and a 7.4% absolute reduction in diabetes incidence among South Asian origin people receiving lifestyle modification interventions as compared with controls.
- Effects were consistent for all a priori pre-specified subgroups.
- Modest effects were found for 2-hour glucose, weight, and waist circumference, consistent across all pre-specified subgroups, except for weight by region.

How might this impact on clinical practice in the foreseeable future

- Given the substantial and growing burden of diabetes, particularly in South Asian origin populations, this meta-analysis strongly supports the importance of lifestyle modification interventions as part of a strategy to prevent diabetes in these populations.

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Introduction

Type 2 diabetes (diabetes) and its complications constitute a major threat to global health. Populations of South Asian origin have at least a two to four times higher risk than European origin populations [1, 2] and develop diabetes and its complications at a younger age [3, 4]. Patterns of fat deposition, low lean mass [5], and low birth weight [6], are considered to contribute to early-onset insulin resistance and diabetes in South Asians, exacerbated by changing lifestyle, urbanization and migration. Further, the proportion of deaths attributable to diabetes is almost 50% higher in South Asians than in populations of European origin, with no clear signs that the risk will level off over time [7]. Therefore, adequate actions for prevention of diabetes among South Asians are imperative.

From 2001, efficacy trials have documented up to 58% reduction in diabetes incidence in high-risk adults through lifestyle modification interventions incorporating a healthy diet and/or physical activity [8-12]. Recent meta-analyses of efficacy and pragmatic diabetes prevention trials found a 30-40% reduction in diabetes incidence [13, 14]. However, none of these meta-analyses reported effects specifically for South Asians [13, 14], although several lifestyle interventions trials have been developed and tested, culturally adapted to suit the specific needs, cultural norms and values of the South Asian populations in different contexts [15-18]. Although some trials appeared moderately successful, effectiveness differed across studies. Although a few previous reviews have explored effects of lifestyle modification interventions on glucose measures and anthropometric outcomes in South Asians [19], many were narrative and limited by inconsistent outcome reporting, and none reported estimates for diabetes incidence [20]. Due to small numbers in individual studies and low power, either because of an a priori too optimistic estimation of effects, or due to drop-out, or lower incidences than expected, the strength of the evidence of individual studies is therefore limited, and the further exploration of effects (e.g. subgroup analyses) are hampered.

Given the current knowledge gap about the effectiveness of lifestyle modification interventions in this high-risk population, we aimed to assess the overall effect from randomised controlled trials with lifestyle interventions with dietary modification and/or physical activity to prevent diabetes in adult South Asians, using individual participant data meta-analysis [21]. In addition, we explored if the effects differed by sex, BMI, age, study duration, and study region.

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Methods

The plan for this individual participant data meta-analysis was registered with the International Prospective Register of Systematic reviews (PROSPERO registration CRD42017078003). The reporting is in line with The Preferred Reporting Items for Systematic reviews and Meta-Analysis of Individual Participant Data [22].

Eligibility criteria We included randomised controlled trials that compared the effect of lifestyle modification interventions incorporating a healthy diet and/or physical activity with usual care/control groups not receiving the lifestyle intervention to prevent diabetes in the South Asian adult population (≥18 years) worldwide. To reduce the risk of bias in the estimates, studies were only included if judged to be at least of moderate quality by the Quality Assessment Tool for Quantitative Studies (see below) [23]. We a priori decided to exclude studies exclusively on drugs and surgical interventions, alone, or in combination with lifestyle modification, or evaluating physical activity components not consisting of cardio-vascular exercise (e.g., yoga) as the only physical activity component, or single dietary components (such as vitamin D supplementation).

Search strategy We searched PubMed, Embase, Cochrane Library and Web of Science, first from the start to September 30th 2017 to allow for inclusion of studies for the individual participant data meta-analysis (search strategy: Electronic supplementary material (ESM)), supplemented with reference list tracing of key reviews [19, 20, 24, 25], included studies [12, 15-18, 26], and by searching trial registers. The search was updated on September 24th 2018. The work builds on and complements our previous narrative systematic review of dietary and physical activity components recommended in experimental, quasi-experimental and before-after studies to prevent diabetes in South Asians [27].

Study selection and risk of bias assessment Two reviewers independently screened titles and abstracts for eligibility, thereafter full-texts. The risk of bias was assessed at the study level using the Quality Assessment Tool for Quantitative Studies [23] by three reviewers as we perceived the quality assessment tool to be vulnerable to differences in interpretation. For all processes, a discussion was held in case of discrepancies to reach consensus. Only studies judged to be at least of moderate quality were included [23].

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Data extraction Information on study design and population characteristics was extracted from published manuscripts, study protocols, and personal communication with authors, using a piloted extraction form, by two reviewers working independently [27]. A discussion was held in case of discrepancies, and a third independent reviewer arbitrated, if necessary. Principal investigators of eligible studies published prior to September 30th 2017 were contacted for permission to include individual participant data on sex, age, anthropometric measures, and fasting, and 2-hour glucose, from oral glucose tolerance tests. To allow for transformation and analysis, the deadline for data inclusion was set to March 1st 2018. After ethical approval for this study from each primary study, data transfer agreements were signed before we received anonymized individual level data.

Data analysis and quality of the evidence The primary outcome was diabetes incidence, defined as fasting glucose ≥ 7.0 mmol/l, and/or 2 hour-glucose ≥ 11.1mmol/l, or registered as doctor diagnosed by self-report at follow-up visits [12, 16, 26]. Secondary intermediate outcomes were changes in fasting glucose, 2 hour-glucose, body weight (kg), and waist circumference (cm). Except for one study with age stratified into nine groups [16], we used age in years. Analyses were based on an intention-to-treat approach. All principal investigators confirmed preliminary analyses after variable standardization and data cleaning.

Cox proportional hazards models were used to estimate age-adjusted hazard ratios of diabetes incidence. The proportional hazard assumption was tested separately for each covariate and also overall (global test) and found to be met. The three studies with men and women were also adjusted for sex. Time to diabetes was used as the dependent variable in our survival analysis, and calculated from the trial start date to either the diabetes diagnosis, or the end of each trial. For secondary outcomes, we determined mean differences with 95% CIs, adjusted for baseline values for the outcome variable of interest, age, and sex when relevant, using the last available estimate [21]. Individual participant data meta-analyses were done in two stages. First, mixed regression models with random effects at individual level and group allocation as fixed-effect were performed for each study. For secondary outcomes, we used generalized linear models with identity link function for studies with only one follow-up visit [17, 18]. Secondly, estimates from the multilevel models were used to estimate weighted averages across studies. We used the I-squared statistics to express the amount of variance attributable to study heterogeneity. A priori defined subgroup analyses were performed for sex, baseline BMI ≥ 27.5 kg/m^2 or below, age > 44 years or below, short (5-7 months) and long-term (2-3 years) study duration, and region, testing for interactions between subgroups. We used Stata version 15.1 for the regression analyses for each study, and to generate weighted estimates across studies, and the metafor package in R for the forest plots. Due to loss to follow-up in some studies, we performed a sensitivity analysis applying within-trial multiple imputations [28]. In trials with multiple follow-up visits [15, 16, 26] we used REALCOM-IMPUTE [29] to account for correlation between repeated measures. In trials with one follow-up [17, 18] we used the Multiple Imputation by Chained Equations [30]. For each trial, we created 20 imputed datasets, thereafter combined for pooled estimates. We also performed funnel plots to visually explore possible publication bias/small study effect.

Finally, we used the GRADE approach to rate the quality of evidence and to generate absolute effect estimates for the outcomes [31]. In our previous systematic review, we identified randomized controlled trials that ended until 2015 and had not published results or updated their registrations [27]. Of the six that were identified and that might have been eligible for the individual participant data meta-analysis, three have not yet reported, one has since published results [32], and two are still ongoing. Although it is unclear if the underreporting is related to unsuccessful inclusion or negative results, it is indicative of a probable publication bias.

Results

Description of included studies We identified 4240 publications and, after removal of duplicates, 3009 titles and abstracts were screened, of which 2983 were excluded (Flow chart; ESM Figure 1). Following full-text review of 17 articles, six randomized controlled trials fulfilled the inclusion criteria for the individual participant data meta-analysis [12, 15-18, 26]. Characteristics of excluded studies [32-42] are given in ESM Table 1. We obtained individual participant data for all six eligible studies for the meta-analysis (Table 1). When cleaning the data for analyses we identified 29 cases from two studies with glucose levels indicative of diabetes at inclusion [17, 18]. These cases were excluded, leaving 1816 participants, of whom 604 (33%) were female. Three studies included both sexes, two were in males [18, 26], and one in females only [17]. Four studies were of 2-3 years duration [12, 15, 16, 26], while two lasted 5-7 months [17, 18]. Four studies were from Europe [15-18] and two from India [12, 26]. Five studies combined a dietary and physical activity intervention [12, 15-17, 26], while one used physical

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activity only (primarily floorball/field hockey) [18]. Individual and/or group-based educational sessions were provided with varying intensity, one supported by mobile phone messages [26]. One study offered home visits from a dietitian and involvement of family members [16], three were performed in the community [15, 17, 18], and the two Indian studies were performed in a workplace setting [12, 26]. The quality of five studies was rated as strong (ESM Table 2).

Loss to follow-up differed from more than 20% in two studies [15, 17] of 7 months and 2 years duration, to 0-2.3% in other studies that had 3 years duration [12, 16] (ESM Table 3). No clear patterns of differences in baseline characteristics between the intervention and control groups were observed (ESM Table 4). The age range at inclusion was 18-80 years, with mean age differing from 37 [18] to 52 years [16]. The mean BMI differed from 26 kg/m^2 in the Indian studies [12, 26] to 30.6 kg/m^2 in one European study [16]. At baseline, mean 2-hour glucose levels were highest in the Indian studies, which only included participants with persistently impaired glucose tolerance [12, 26].

Diabetes incidence Incident diabetes was observed in 118 of 936 (12.6%) participants in the intervention group and in 176 of 880 (20.0%) participants in the control group (adjusted hazard ratio 0.65 (95% CI 0.51 to 0.81; p=0.0002, I^2=0%) (Table 2 and Figure 1). This reflects an absolute reduction of 7.4% (95% CI 4.0-10.2) and a number needed to treat (NNT) of 14 (95% CI 10.0 -28.0). In subgroup analyses, we did not find differences in relative estimates of effects by sex, age, BMI, study duration, or region. For the long-term studies, the estimates were identical after exclusion of one study [15] with high loss to follow-up (0.65, (95% CI 0.51 to 0.83, p=0.0004)). Overall, and for subgroups, we found no (I^2=0%), or low, between-study heterogeneity. According to GRADE the quality of evidence can be rated as moderate; quality was rated down due to some, but overall limited, concerns of risk of bias (e.g. lacking blinding of participants and providers), and possible publication bias, although not confirmed by visual inspection of funnel plots (data not shown).

Other outcomes For secondary outcomes, we observed a reduction in 2-hour glucose (-0.34 mmol/l, 95% CI -0.62 to -0.04; p=0.02, I^2=51%), weight (-0.75 kg, 95% CI -1.34 to -0.17; p=0.01, I^2=72%), and waist circumference (-1.16 cm, 95% CI -2.16 to -0.16; p=0.02, I^2=74%) in the intervention versus control group (Table 3 and EMS Figure 2), with

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no effect for fasting glucose (-0.03, 95% CI -0.16 to 0.16, p=0.37, I^2=27%). No consistent subgroups differences in effects were found for secondary outcomes (ESM Table 5), although a difference in effect for weight (-1.10 kg versus -0.08 kg, p=0.02 for interaction) was revealed for European versus Indian studies, with a similar but non-significant effect estimate for waist circumference (-1.59 cm vs -0.26 cm, p=0.09 for interaction). The GRADE quality of evidence for 2-hour glucose was rated as moderate, rated down due to some concerns of risk of bias. For the other secondary outcomes, the quality was considered low due to imprecision and/or heterogeneity between studies (ESM Table 5). Sensitivity analyses after multiple imputations yielded similar effect estimates as the main analysis for secondary outcomes, although CIs were slightly wider, and the result for weight was only borderline significant (p =0.06; results not shown). Lastly, the distribution curves for fasting and 2-hour glucose at the last visit for all studies merged, showed a larger shift to the right in the control than in the intervention group (ESM Figure 3). In the intervention group, 4.5% had developed diabetes at the last follow-up based on fasting glucose values ≥ 7.0 mmol/l, and 8.2% based on fasting glucose values ≥ 11.1 mmol/l, compared with 7.5% (p=0.017) and 14.9% (p <0.0001) respectively in the control group.

Discussion

In this individual participant data meta-analysis we found that the overall incidence of diabetes was reduced by 35% in the lifestyle modification intervention compared with the control group, with an absolute risk reduction of 7.4%, and a number needed to treat of ~14 over a mean of two years. Results for diabetes were consistent for males and females and for other key subgroups. The studies included participants with normal and impaired glucose regulation and a range of age and BMI values at baseline, indicating high external validity. We also found evidence of a modest effect on 2-hour glucose and simple adiposity (weight and waist circumference) measures. Of note, however, at the last follow-up we observed both for fasting and 2-hour glucose a stronger shift on the right side of the distribution curve in the control groups, with significantly more diabetes cases, compared to the intervention groups.

The main strength of this study is that it is the first to report summary effects of lifestyle interventions on diabetes incidence in the high-risk South Asian population. Starting with a systematic review of the literature, we used individual participant data meta-analysis from all the six eligible randomized controlled trials among South

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Asians published prior to the inclusion date, to produce precise summary effects overall and across subgroups [21], also for our secondary outcomes fasting and 2-hour glucose and adiposity measures. Compared with meta-analyses based on aggregate data on study level from published papers, individual participant data meta-analysis facilitates standardisation of analyses, increases the precision of estimates and the quality of subgroup analyses [21]. Further, assessing the quality of evidence according to GRADE, we systematically and transparently assessed all factors that could impact on our certainty in the effects estimates, including risk of bias in each study, heterogeneity, indirectness, imprecision, and publication bias [31].

However, our review is limited by a relatively small number of trials, some with high loss to follow-up, and relatively little variation in settings. The included studies counted approximately 300 incident cases of diabetes, the majority (83%) from the Indian studies. Thus, the power to detect subgroups differences and to further explore between-study heterogeneity for the adiposity measures was limited. Although we consider the evidence to be generally applicable to the target population, we cannot fully rule out potential indirectness due to differences between populations (country of origin or migrant status), interventions (type, content, intensity, mode of delivery, compliance), and settings (family and community-based versus workplace).

Our meta-analysis included efficacy [12, 16] and more pragmatic trials [15, 17, 18, 26]. The 35% relative risk reduction in diabetes incidence resembles the risk reduction (39%) reported in a standard meta-analysis of 19 efficacy and pragmatic diabetes prevention trials in subjects with impaired glucose tolerance or impaired fasting glucose after a mean of 2.6 years active lifestyle intervention [13]. Although ten studies in the latter meta-analysis were conducted in Asia, result for South Asians were not reported. Of note, the absolute benefit on diabetes prevention was higher in our study than in this meta-analysis (7.4% vs 4.0%. respectively) and so the NNT was lower (14 versus 25) [13]. Our findings compare well with the first efficacy studies, reporting 6.2-12% absolute risk reductions (NNT 16-8 respectively) [8, 9], but somewhat stronger than in a meta-analysis of translational studies to prevent diabetes in high-risk populations other than South Asians (relative risk reduction: 29%, absolute risk reduction; 3%) [14].

Meta-analysis of diabetes prevention trials indicated that dietary and physical activity interventions combined were more effective than either strategies alone, but the number of studies was limited for single strategy studies [13]. Although more studies to date seems to indicate that the dietary interventions are more

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effective than physical activity interventions to reduce diabetes incidence in high risk individuals, the potential of physical activity interventions may be underestimated due to shortcomings in the type, intensity and mode of delivery. Although we could not assess this, the intensity of the interventions in the long-term studies in our review was lower [12, 26] or comparable [16] to those of the first efficacy studies which had stronger effects [8, 9]. Even a low-cost community-based peer-support lifestyle intervention program published too late to be included in our study, found a 12% relative reduction in diabetes incidence in individuals with a high Indian Diabetes Risk Score [32]. The smaller effect might be partly attributed to the selection of participants, with the majority having normoglycemia or isolated impaired fasting glucose at baseline, as there are no proven interventions so far to reduce diabetes incidence in such subjects [32].

In contrast to our finding of an overall 35% reduction on diabetes incidence with a relative small mean 0.75 kg reduction in weight, studies in other populations found weight reduction to be the main driver of the effect [8, 9, 13], i.e. 16% reduction in diabetes incidence for each kg of weight loss [43]. Of note, despite small changes in mean weight and waist circumference values, both for fasting glucose (primarily reflecting hepatic insulin resistance) and 2-hour glucose (reflecting muscle insulin resistance), the intervention had a more profound effect on the right side of the distribution curve, indicating a reduced insulin resistance [44]. Further, achievements of dietary and physical activity goals, even without weight loss, may improve 2-hour glucose and reduce diabetes incidence [8], as found in the Indian studies in our review [12, 26], where a reduction in portion size, consumption of carbohydrates and oil intake was related to a lower diabetes incidence even without weight loss [38]. Although trials among South Asians are few, there are indications that improvements in the quality of the diet (more complex carbohydrates, monounsaturated and polyunsaturated fatty acids) might improve blood glucose, serum insulin, lipids, inflammatory markers and hepatic fat [5].

Although only 33% of participants were females in our meta-analysis, as previous studies were underpowered to study potential sex differences, an important new finding was that their diabetes incidence was significantly reduced, despite a slightly smaller non-significant effect estimate for 2-hour glucose, weight, and waist circumference than in males. Furthermore, the larger effect on weight, with a concomitant non-significant effect estimate for waist circumference in the European than in the Indian studies in our meta-analysis is noteworthy. This may reflect different phenotypes, as it would be easier to achieve a larger reduction in weight measures

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amongst South Asians residing in Europe, who had higher BMIs, but differences in the diet and/or physical activity level at baseline or induced by the intervention may also be involved. Furthermore, perceptions of weight and health are changing across generations, and differ by region [45]. South Asians living in Europe, particularly females, may be more sensitized to the importance of weight loss than those living in their country of origin [46]. Others report that sex did not influence the effects of lifestyle interventions [13], and lifestyle trials aimed at weight loss which explored sex differences in anthropometric outcomes, mostly report stronger effects in males, but actual sex differences were small [47]. Thus, there is little evidence yet to indicate that males and females generally should adopt different weight loss strategies.

As the studies outside India in our meta-analysis, conducted mostly among first-generation South Asian migrants in Europe, had suggested only a modest effect, comparable and clinically important effects on diabetes incidence regardless of region have important implications for policymakers and clinicians. The consistency of effects across subgroups of the South Asian population at risk of diabetes has made us rethink, contrary to our priori beliefs based on the outcomes of single studies, that benefits actually may be achieved by lifestyle modification interventions, not only under ideal conditions, but also in real-life settings [15, 17, 18, 26]. Cultural adaptations to mode of delivery may be necessary across contexts as cultural adaptations likely promote the effectiveness of interventions among specific ethnic populations [48, 49], although evidence of effects of cultural targeting on diabetes prevention outside India is still scarce [50]. Interestingly, one study using a culturally targeted physical activity intervention (floorball/field hockey) for men provided strong results for all secondary outcomes, although limited by its small size and short duration [18].

There are, however, several unanswered questions that should be addressed. First, lifestyle intervention studies have used generic recommendations (i.e. based on those for the local majority population) [27], while different targets for dietary and physical activity recommendations may be necessary [27, 51]. Further work is required on the mechanisms by which these interventions are having their effect, including the role and type of physical activity, diet quality, specific dietary components, cooking practices and timing of meals [52]. Further, we predict that larger effects on diabetes risk in South Asians might be achieved in studies aiming at larger weight reductions [53, 54], and with more intense dietary and physical activity changes [51]. Reach, retention and long-term sustainability may be enhanced through improvements in targeting and delivery, and benefits in the longer term (beyond two to three years) should be further investigated. Hopefully, ongoing studies will be complemented with new high quality trials addressing the issues outlined above. Future systematic reviews should be extended to explore effects by mode of delivery, intensity and contextual factors. In addition to high-risk strategies, there are strong recommendations for population-based strategies as part of national public health policies [52].

In conclusion, pending deeper understanding of the causation of diabetes in South Asians, and the development of new kinds of interventions, this individual participant data meta-analysis of lifestyle modification interventions in South Asian populations at high risk of diabetes provides evidence of a clinically important 35% relative reduction in diabetes incidence, with a NNT of 14 to prevent one case of diabetes over a mean of two years. Given the substantial and growing burden of diabetes, particularly in South Asian origin populations, this meta-analysis provides support for ongoing strategies underpinned by weight loss, dietary change and increased physical activity to prevent type 2 diabetes. Future work should aim to understand the mechanisms by which these effects occur, evaluate cost effectiveness, and develop more effective interventions.

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Data availability The data of the individual studies were obtained through the principal investigators of the individual studies for the purpose of the current analysis only, after a formal collaboration and data transfer agreement was signed. This contract restricts the further dissemination of data to third parties. The team of the current study may be contacted with further questions about these procedures. Additionally, researchers interested in the data of the individual studies may contact the principal investigators of the respective trials with their data requests.

Authors' contributions and study guarantor

The present study builds on a previous systematic review in which the corresponding author was involved. RSB, KS and IvV conceived and initiated the meta-analysis, and AKJ and IvV designed the current study. All authors (except RSB) were presented for, and agreed on, the protocol for analysis. MM and IvV screened abstracts and later full-text studies for eligibility, supported by MN when necessary to reach consensus. MM, IvV and CC assessed the quality of eligible studies. Acquisition of data was done by IB and IM. IvV, KS, AR, MK, EA, AD, GC and AS contributed data to the study and verified preliminary results for their respective studies. IB, IM and KRR analysed the data, and together with AKJ, POV and IvV, interpreted the initial results. AKJ and IvV drafted the manuscript, with input from MM, IB, IM and POV. All authors contributed to the interpretations, critically revised the manuscript and approved the last version for publication. IB, IM, KRR and AKJ had full access to all the data in the study.

AKJ is responsible for the integrity of the work as a whole.

Conflicts of Interest All authors met the ICMJE criteria for authorship. Some authors contributed to studies that were included in this systematic review. JMRG, NS, RSB, AD, and AS were co-authors on the PODOSA trial but were not involved in its evaluation in the present paper. MN, IvV and KS contributed to DH!AAN, and were therefore not involved in the quality assessment in the present paper. Similarly, no other co-authors that contributed with their data (AR, MK, EA) were involved in the quality assessment in the present paper. The authors have filled in the ICMJE form for disclosure of potential conflicts of interest. We declare no conflict of interest.

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References

1. Sattar N, Gill JMR. Type 2 diabetes in migrant south Asians: mechanisms, mitigation, and management. The Lancet Diabetes & Endocrinology.3(12):1004-16.
2. Jenum AK, Diep LM, Holmboe-Ottesen G, Holme IM, Kumar BN, Birkeland KI. Diabetes susceptibility in ethnic minority groups from Turkey, Vietnam, Sri Lanka and Pakistan compared with Norwegians - the association with adiposity is strongest for ethnic minority women. BMC Public Health. 2012;12:150.
3. Gholap N, Davies M, Patel K, Sattar N, Khunti K. Type 2 diabetes and cardiovascular disease in South Asians. Primary care diabetes. 2011;5(1):45-56.
4. Raymond NT, Varadhan L, Reynold DR, Bush K, Sankaranarayanan S, Bellary S, et al. Higher prevalence of retinopathy in diabetic patients of South Asian ethnicity compared with white Europeans in the community: a cross-sectional study. Diabetes Care. 2009;32(3):410-5.
5. Gulati S, Misra A. Abdominal obesity and type 2 diabetes in Asian Indians: dietary strategies including edible oils, cooking practices and sugar intake. Eur J Clin Nutr. 2017;71(7):850-7.
6. Krishnaveni GV, Yajnik CS. Developmental origins of diabetes-an Indian perspective. Eur J Clin Nutr. 2017;71(7):865-9.
7. Ikram UZ, Kunst AE, Lamkaddem M, Stronks K. The disease burden across different ethnic groups in Amsterdam, the Netherlands, 2011-2030. European journal of public health. 2014;24(4):600-5.
8. Tuomilehto J, Lindström J, Eriksson JG, Valle TT, Hämäläinen H, Ilanne-Parikka P, et al. Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance. N Engl J Med. 2001;344.
9. Knowler WC, Barrett-Connor E, Fowler SE, Hamman RF, Lachin JM, Walker EA, et al. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. N Engl J Med. 2002;346.
10. Pan XR, Li GW, Hu YH, Wang JX, Yang WY, An ZX, et al. Effects of diet and exercise in preventing NIDDM in people with impaired glucose tolerance: the Da Qing IGT and diabetes study. Diabetes Care. 1997;20.
11. Kosaka K, Noda M, Kuzuya T. Prevention of type 2 diabetes by lifestyle intervention: a Japanese trial in IGT males. Diabetes Res Clin Pract. 2005;67(2):152-62.
12. Ramachandran A, Snehalatha C, Mary S, Mukesh B, Bhaskar AD, Vijay V, et al. The Indian Diabetes Prevention Programme shows that lifestyle modification and metformin prevent type 2 diabetes in Asian Indian subjects with impaired glucose tolerance (IDPP-1). Diabetologia. 2006;49(2):289-97.
13. Haw JS, Galaviz KI, Straus AN, Kowalski AJ, Magee MJ, Weber MB, et al. Long-term Sustainability of Diabetes Prevention Approaches: A Systematic Review and Meta-analysis of Randomized Clinical Trials. JAMA internal medicine. 2017;177(12):1808-17.
14. Galaviz KI, Weber MB, Straus A, Haw JS, Narayan KMV, Ali MK. Global Diabetes Prevention Interventions: A Systematic Review and Network Meta-analysis of the Real-World Impact on Incidence, Weight, and Glucose. Diabetes Care. 2018;41(7):1526-34.
15. Admiraal WM, Vlaar EM, Nierkens V, Holleman F, Middelkoop BJ, Stronks K, et al. Intensive lifestyle intervention in general practice to prevent type 2 diabetes among 18 to 60-year-old South Asians: 1-year effects on the weight status and metabolic profile of participants in a randomized controlled trial. PloS one. 2013;8(7):e68605.
16. Bhopal RS, Douglas A, Wallia S, Forbes JF, Lean MEJ, Gill JMR, et al. Effect of a lifestyle intervention on weight change in south Asian individuals in the UK at high risk of type 2 diabetes: A family-cluster randomised controlled trial. The Lancet Diabetes and Endocrinology. 2014;2(3):218-27.
17. Telle-Hjellset V, Kjollesdal MKR, Bjorge B, Holmboe-Ottesen G, Wandel M, Birkeland KRI, et al. The InnvaDiab-DE-PLAN study: a randomised controlled trial with a culturally adapted education programme improved the risk profile for type 2 diabetes in Pakistani immigrant women. British Journal of Nutrition. 2013;109(3):529-38.
18. Andersen E, Burton NW, Anderssen SA. Physical activity levels six months after a randomised controlled physical activity intervention for Pakistani immigrant men living in Norway. International journal of behavioral nutrition and physical activity [Internet]. 2012; 9:[47 p.]. Available from: http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/394/CN-00840394/frame.htmlhttp://www.ncbi.nlm.nih.gov/pmc/articles/PMC3419654/pdf/1479-5868-9-47.pdf.

19. Brown T, Smith S, Bhopal R, Kasim A, Summerbell C. Diet and physical activity interventions to prevent or treat obesity in South Asian children and adults: a systematic review and meta-analysis. International journal of environmental research and public health. 2015;12(1):566-94.
20. Chapman J, Qureshi N, Kai J. Effectiveness of physical activity and dietary interventions in South Asian populations: a systematic review. The British journal of general practice : the journal of the Royal College of General Practitioners. 2013;63(607):e104-14.
21. Riley RD, Lambert PC, Abo-Zaid G. Meta-analysis of individual participant data: rationale, conduct, and reporting. Bmj. 2010;340:c221.
22. Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015;349.
23. Thomas H. Quality Assessment Tool for Quantitative Studies.: Effective Public Health Practice Project, McMaster University: Hamilton, ON, Canada; 2003.
24. Chowdhury TA, Hitman GA. Type 2 diabetes in people of South Asian origin: potential strategies for prevention. The British Journal of Diabetes & Vascular Disease. 2007;7(6):279-82.
25. Ramachandran A, Snehalatha C, Samith Shetty A, Nanditha A. Primary prevention of Type 2 diabetes in South Asians--challenges and the way forward. Diabet Med. 2013;30(1):26-34.
26. Ramachandran A, Snehalatha C, Ram J, Selvam S, Simon M, Nanditha A, et al. Effectiveness of mobile phone messaging in prevention of type 2 diabetes by lifestyle modification in men in India: a prospective, parallel-group, randomised controlled trial. The lancet Diabetes & endocrinology. 2013;1(3):191-8.
27. Muilwijk M, Nicolaou M, Qureshi SA, Celis-Morales C, Gill JMR, Sheikh A, et al. Dietary and physical activity recommendations to prevent type 2 diabetes in South Asian adults: A systematic review. PloS one. 2018;13(7):e0200681.
28. Koopman L, van der Heijden GJ, Grobbee DE, Rovers MM. Comparison of methods of handling missing data in individual patient data meta-analyses: an empirical example on antibiotics in children with acute otitis media. Am J Epidemiol. 2008;167(5):540-5.
29. Carpenter JR; HGHKM. REALCOM-IMPUTE Software for Multilevel Multiple Imputation with Mixed Response Types. Journal of Statistical Software. 2011;45(5):1-14.
30. Multiple Imputation by Chained Equations (MICE): Implementation in Stata. Journal of Statistical Software. 2011;45(5):1-20.
31. Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. Bmj. 2008;336(7650):924-6.
32. Thankappan KR, Sathish T, Tapp RJ, Shaw JE, Lotfaliany M, Wolfe R, et al. A peer-support lifestyle intervention for preventing type 2 diabetes in India: A cluster-randomized controlled trial of the Kerala Diabetes Prevention Program. PLoS Med. 2018;15(6):e1002575.
33. Mayer-Davis EJ, Sparks KC, Hirst K, Costacou T, Lovejoy JC, Regensteiner JG, et al. Dietary intake in the diabetes prevention program cohort: baseline and 1-year post randomization. Annals of epidemiology. 2004;14(10):763-72.
34. Snehalatha C, Mary S, Joshi VV, Ramachandran A. Beneficial effects of strategies for primary prevention of diabetes on cardiovascular risk factors: results of the Indian Diabetes Prevention Programme. Diabetes & vascular disease research. 2008;5(1):25-9.
35. Snehalatha C, Mary S, Selvam S, Sathish Kumar CK, Shetty SB, Nanditha A, et al. Changes in insulin secretion and insulin sensitivity in relation to the glycemic outcomes in subjects with impaired glucose tolerance in the Indian Diabetes Prevention Programme-1 (IDPP-1). Diabetes Care. 2009;32(10):1796-801.
36. Ramachandran A, Arun N, Shetty AS, Snehalatha C. Efficacy of primary prevention interventions when fasting and postglucose dysglycemia coexist: analysis of the Indian Diabetes Prevention Programmes (IDPP-1 and IDPP-2). Diabetes Care. 2010;33(10):2164-8.
37. Patel JV, Hughes EA, Lip GY, Gill PS. Diabetes Health, Residence & Metabolism in Asians: the DHRMA study, research into foods from the Indian subcontinent - a blinded, randomised, placebo controlled trial. BMC cardiovascular disorders. 2011;11:70.
38. Ram J, Selvam S, Snehalatha C, Nanditha A, Simon M, Shetty AS, et al. Improvement in diet habits, independent of physical activity helps to reduce incident diabetes among prediabetic Asian Indian men. Diabetes Res Clin Pract. 2014;106(3):491-5.

Diabetologia https://doi.org/10.1007/s00125-019-4905-2 (Published online 15 June 2019)

39. Weber MB, Ranjani H, Staimez LR, Anjana RM, Ali MK, Narayan KM, et al. The Stepwise Approach to Diabetes Prevention: Results From the D-CLIP Randomized Controlled Trial. Diabetes Care. 2016;39(10):1760-7.
40. Willis A, Roshan M, Patel N, Gray LJ, Yates T, Davies M, et al. A community faith centre based screening and educational intervention to reduce the risk of type 2 diabetes: A feasibility study. Diabetes Res Clin Pract. 2016;120:73-80.
41. Patel RM, Misra R, Raj S, Balasubramanyam A. Effectiveness of a Group-Based Culturally Tailored Lifestyle Intervention Program on Changes in Risk Factors for Type 2 Diabetes among Asian Indians in the United States. Journal of diabetes research. 2017;2017:2751980.
42. Wijesuriya M, Fountoulakis N, Guess N, Banneheka S, Vasantharajah L, Gulliford M, et al. A pragmatic lifestyle modification programme reduces the incidence of predictors of cardio-metabolic disease and dysglycaemia in a young healthy urban South Asian population: a randomised controlled trial. BMC medicine. 2017;15(1):146.
43. Hamman RF, Wing RR, Edelstein SL, Lachin JM, Bray GA, Delahanty L, et al. Effect of weight loss with lifestyle intervention on risk of diabetes. Diabetes Care. 2006;29(9):2102-7.
44. Engberg S, Glumer C, Witte DR, Jorgensen T, Borch-Johnsen K. Differential relationship between physical activity and progression to diabetes by glucose tolerance status: the Inter99 Study. Diabetologia. 2010;53(1):70-8.
45. Patel S, Bhopal R, Unwin N, White M, Alberti KG, Yallop J. Mismatch between perceived and actual overweight in diabetic and non-diabetic populations: a comparative study of South Asian and European women. J Epidemiol Community Health. 2001;55(5):332-3.
46. Hussain A, Bjorge B, Hjellset VT, Holmboe-Ottesen G, Wandel M. Body size perceptions among Pakistani women in Norway participating in a controlled trial to prevent deterioration of glucose tolerance. Ethnicity & health. 2010;15(3):237-51.
47. Williams RL, Wood LG, Collins CE, Callister R. Effectiveness of weight loss interventions--is there a difference between men and women: a systematic review. Obesity reviews : an official journal of the International Association for the Study of Obesity. 2015;16(2):171-86.
48. Davidson EM, Liu JJ, Bhopal R, White M, Johnson MR, Netto G, et al. Behavior change interventions to improve the health of racial and ethnic minority populations: a tool kit of adaptation approaches. The Milbank quarterly. 2013;91(4):811-51.
49. Kreuter MW, Lukwago SN, Bucholtz RD, Clark EM, Sanders-Thompson V. Achieving cultural appropriateness in health promotion programs: targeted and tailored approaches. Health education & behavior : the official publication of the Society for Public Health Education. 2003;30(2):133-46.
50. Nierkens V, Hartman MA, Nicolaou M, Vissenberg C, Beune EJ, Hosper K, et al. Effectiveness of cultural adaptations of interventions aimed at smoking cessation, diet, and/or physical activity in ethnic minorities. a systematic review. PloS one. 2013;8(10):e73373.
51. Iliodromiti S, Ghouri N, Celis-Morales CA, Sattar N, Lumsden MA, Gill JM. Should Physical Activity Recommendations for South Asian Adults Be Ethnicity-Specific? Evidence from a Cross-Sectional Study of South Asian and White European Men and Women. PloS one. 2016;11(8):e0160024.
52. Bhopal RS. Epidemic of Cardiovascular Disease and Diabetes. Explaining the Phenomenon in South Asians Worldwide. Oxford: Oxford University Press; 2019 (in press). 334 p.
53. Lean ME, Leslie WS, Barnes AC, Brosnahan N, Thom G, McCombie L, et al. Primary care-led weight management for remission of type 2 diabetes (DiRECT): an open-label, cluster-randomised trial. Lancet. 2018;391(10120):541-51.
54. Huttunen-Lenz M, Hansen S, Christensen P, Meinert Larsen T, Sando-Pedersen F, Drummen M, et al. PREVIEW study-influence of a behavior modification intervention (PREMIT) in over 2300 people with pre-diabetes: intention, self-efficacy and outcome expectancies during the early phase of a lifestyle intervention. Psychology research and behavior management. 2018;11:383-94.

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Table 1 Randomized controlled trials included in the individual participant data meta-analysis

Study ID	Countr y	Ethnicity	Size (n)	Age (years)	Sex (% men)	Inclusion criteria	Duration (months)	Mode of delivery of intervention	Components		Setting
									Diet	PA	
IDPP-1 (2006)[12]	India	Indians	253	35-56	76.3	IGT after 2 OGTTs	36	Personal sessions every 6 months, calls 1 / month	Based on dietary guidelines for Indians	30 min brisk walking daily	Workplace
PAMH (2012)[18]	Norway	Pakistani	139	25-60	100	Not regularly physically active, free of diagnosed diabetes	5	Physiologist-led group exercise session (floorball≠) (2x / week), 1x1h individually counselling session, 2 group lectures and follow-up phone call	No specific dietary recommendatio ns	30 min PA daily	Community
Innva-DiabDE-PLAN (2013)[17]	Norway	Pakistani	180	25-62	0	Free of diagnosed diabetes or CVD	7	Educational 2-hour sessions (6x / 7months)	Carbohydrate, sugar, whole grain, legumes and types of fat recommendatio ns	60 min 2 days/week (5000 steps). Walking groups.	Community
DHIAAN (2013)[15]	Nether-lands	South Asian Surinames e	536	18-60	49.2	IFG or IGT, or HbA1c 42-46 mmol/l, or HOMA-IR ≥2.39	12/24*	Dietitian, motivational interviewing (8-10x / 1 year), family session, cooking class, supervised PA program	Fat, fibre, fruit, vegetable and breakfast recommendatio ns, based on national data.	30 min PA daily	Community
Indian SMS Study (2013)[26]	India	Indians	537	35-55	100	BMI≥23 kg/m^2 and IGT after 2 OGTTs	24	Baseline educational session, 2-4 mobile phone messages/week	Based on dietary guidelines for Indians	30 min brisk walking daily	Workplace

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PODOSA (2014)[16]	Scot-land	South Asian	171	35-80	45.6	Waist ≥90 cm men/ ≥80 cm women and IGT or IFG	36	Dietitian(15 home visits over3 years), involvement of family volunteers, annual group sessions	Calorie-deficit diet, based on Finnish DPS [8]	30 min brisk walking daily	Family/home-based

*Quality assessment is based on published paper for results after 12 months, but we also have IPD after 24 months. IGT: Impaired glucose, IFG: Impaired fasting glucose. OGTT: Oral glucose tolerance ≠ floor ball is close to field hockey/land hockey, but played indoor.

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Table 2 Diabetes risks overall and within pre-specified subgroups

Outcome	No. of studies	All cases/N	Intervention n/N	Control n/N	Hazard ratio* (95% CI)	p value†	I^2	p value interaction‡
Overall	6	294/1816	118/936	176/880	0.65 (0.51-0.81)	0.0002	0	
Sex§								
Males	5	244/1211	102/624	142/587	0.68 (0.53-0.88)	0.003	0	0.30
Females	4	50/604	16/312	34/292	0.48 (0.26-0.88)	0.02	0	
BMI								
≥ 27.5 kg/m^2	6	97/729	38/362	59/367	0.64 (0.34-1.20)	0.15	42	0.99
<27.5 kg/m^2	6	197/1087	80/574	117/513	0.64 (0.46-0.88)	0.002	0	
Age								
>44 years	6	170/946	70/481	100/465	0.69 (0.50-0.93)	0.02	0	0.55
≤ 44 years	6	124/870	48/455	76/415	0.59 (0.41-0.85)	0.005	0	
Study duration								
5-7 months	2	4/319	2/177	2/142	0.72 (0.10-5.20)	0.74	0	0.92
2-3 years	4	290/1497	116/759	174/738	0.64 (0.51-0.81)	0.0003	0	
Study region								
Europe	4	50/1026	21/545	29/481	0.69 (0.39-1.21)	0.19	0	0.81
India	2	244/790	97/391	147/399	0.64 (0.49-0.82)	0.0006	0	

* Hazard ratios adjusted for age and sex. † p values for Hazard ratios; ‡ p values for interaction term for subgroup analyses

§ one person in the control group had missing information about sex

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Table 3 Overall effects of lifestyle interventions (mean difference) on continuous outcomes, pooled data with last estimate

Outcome	No. of studies	No. of Participants	Intervention Mean (SD) Kg	Control Mean (SD) Kg	Summary Adjusted MD* (95% CI)	p value†	I^2 (%)
Fasting glucose (mmol/l), last estimate	6	1411	5.5 (0.90)	5.6 (1.15)	-0.03 (-0.10, 0.04)	0.37	27
2-hr glucose (mmol/l), last estimate	6	1428	7.4 (2.44)	8.1 (3.09)	-0.34 (-0.62, -0.07)	0.02	51
Weight (kg), last estimate	6	1479	73.7 (13.08)	74.1 (12.44)	-0.75 (-1.34,-0.17)	0.01	72
Waist (cm), last estimate	6	1462	93.7 (10.18)	94.5 (9.73)	-1.16 (-2.16, -0.16)	0.02	74

*Mean difference based on last estimate (Podosa and IDDP =3 years, DHIAAN and Indian SMS Study= 2 years, InnvaDiab= 7 months and PAMH= 5 months), adjusted for age and baseline values for outcome variable. † p values for mean difference. Analyses are based on participants with at least two measurements. Two studies (DHIAAN, InnvaDiab) had >20% missing data at follow-up (similar for intervention and control group).

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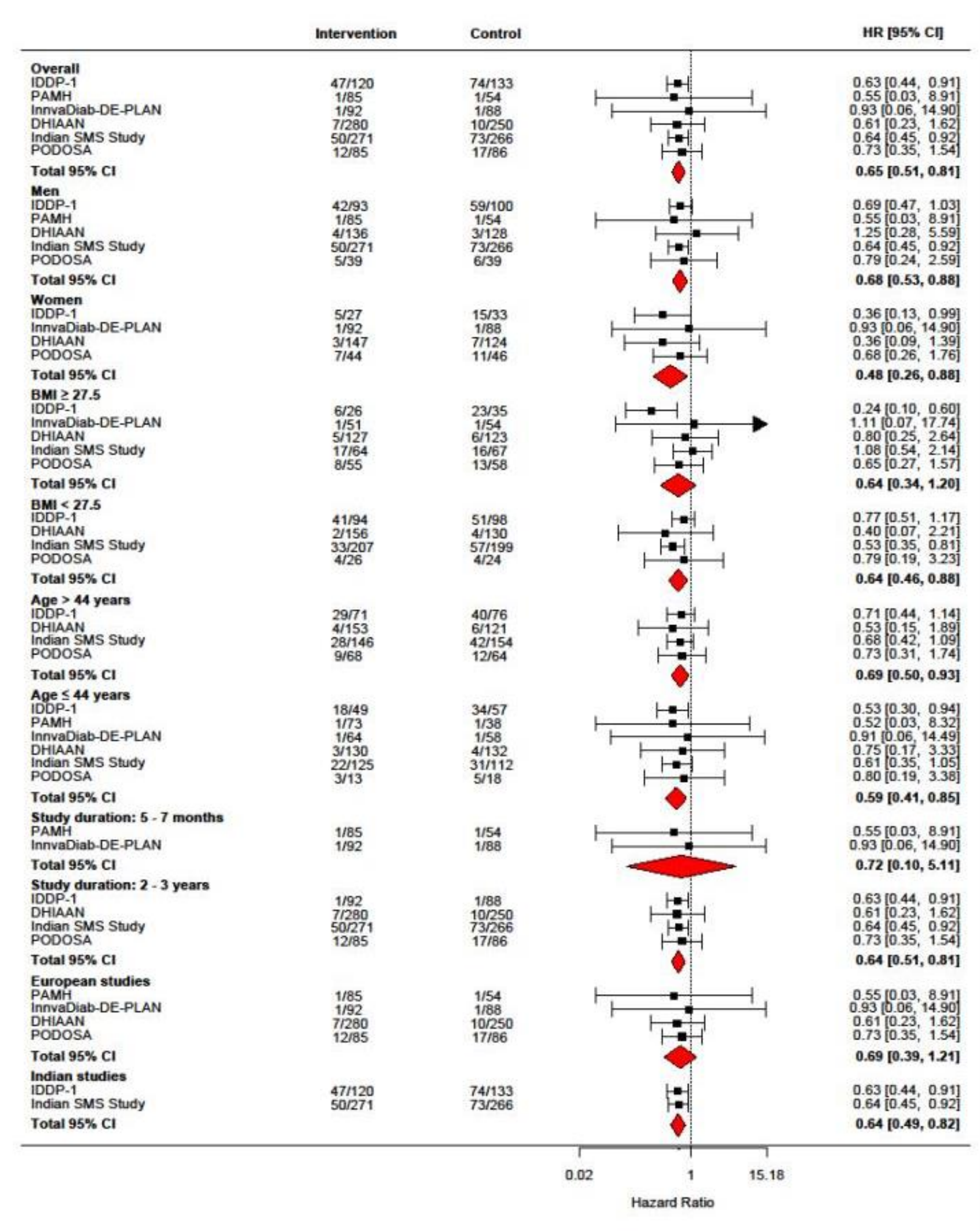

Fig. 1 Forest plot of hazard ratios for diabetes in intervention versus control group, overall and for subgroups – will insert year and references for studies + q statistics.

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ELECTRONIC SUPPLEMENTARY MATERIAL (ESM):

Effects of dietary and physical activity interventions on the risk of type 2 diabetes in South Asians: individual participant data meta-analysis of randomised controlled trials

ESM Search strategy

Pubmed:

(("Asia, Western"[Mesh:NoExp] OR "Bangladesh"[Mesh] OR "Sri Lanka"[Mesh] OR "Nepal"[Mesh] OR "Bhutan"[Mesh] OR "India"[Mesh] OR "Pakistan"[Mesh] OR South Asia*[tiab] OR Asian India*[tiab] OR Pakistan*[tiab] OR Bangladesh*[tiab] OR Sri Lanka*[tiab] OR Nepal*[tiab] OR Bhutan*[tiab] OR India*[tiab]) AND ("Diabetes Mellitus"[Mesh:NoExp] OR "Diabetes Mellitus, Type 2"[Mesh] OR "Overweight"[Mesh] OR "Obesity"[Mesh] OR diabet*[tiab] OR obes*[tiab] OR overweight[tiab] OR weight[tiab]) AND ("Diet"[Mesh] OR "Diet Therapy"[Mesh] OR "Eating"[Mesh] OR "Feeding Behavior"[Mesh:NoExp] OR "Food Habits"[Mesh] OR "diet therapy" [Subheading] OR intake[tiab] OR food*[tiab] OR diet*[tiab] OR nutrition*[tiab] OR eat*[tiab] OR "Exercise"[Mesh] OR "Exercise Therapy"[Mesh] OR "Physical Fitness"[Mesh] OR "Sports"[Mesh] OR activ*[tiab] OR sport*[tiab] OR exercis*[tiab] OR walk*[tiab] OR lifestyle modification[ti]) AND ("Primary Prevention"[Mesh] OR "prevention and control" [Subheading] OR "Guideline" [Publication Type] OR guideline* OR intervention*[tiab] OR advice*[tiab] OR recommendation*[tiab] OR prevent*[tiab] OR promot*[tiab] OR support*[tiab]) AND ("Clinical Trial" [Publication Type] OR "Clinical Trials as Topic"[Mesh] OR "Cohort Studies"[Mesh] OR "Case-Control Studies"[Mesh] OR "Intervention Studies"[Mesh] OR "Feasibility Studies"[Mesh] OR "Case Reports" [Publication Type] OR "Clinical Conference" [Publication Type] OR "Comparative Study" [Publication Type] OR "Consensus Development Conference" [Publication Type] OR "Evaluation Studies" [Publication Type] OR "Meta-Analysis" [Publication Type] OR "Multicenter Study" [Publication Type] OR "Validation Studies" [Publication Type] OR "Observational Study" [Publication Type] OR "Pilot Projects"[Mesh] OR "Controlled Before-After Studies"[Mesh] OR before after stud*[tiab] OR trial[ti] OR controlled[ti] OR random*[tiab] OR intervention*[tiab] OR cohort*[tiab] OR compar*[tiab] OR control*[tiab] OR experimental stud*[tiab])) NOT ("Child"[Mesh] NOT "Adult"[Mesh]) NOT (("Animals"[Mesh] NOT "Humans"[Mesh]) OR "Animals, Laboratory"[Mesh] OR "Animal Experimentation"[Mesh] OR "Models, Animal"[Mesh] OR "Rodentia"[Mesh] OR rat[ti] OR rats[ti] OR mouse[ti] OR mice[ti] OR "Editorial" [Publication Type] OR "Letter" [Publication Type] OR "News" [Publication Type] OR "Comment" [Publication Type] OR "Historical Article" [Publication Type] OR "Anecdotes as Topic"[Mesh] OR letter*[ti] OR comment*[ti] OR abstracts[ti])

Embase (Ovid):

#	Searches
1	south asia/ or bangladesh/ or bhutan/ or india/ or nepal/ or pakistan/ or sri lanka/ or (South Asia* or Asian India* or Pakistan* or Bangladesh* or Sri Lanka* or Nepal* or Bhutan* or India*).ti,ab,kw.
2	*diabetes mellitus/ or *non insulin dependent diabetes mellitus/ or exp *obesity/ or (diabet* or obes* or overweight or weight).ti,ab,kw.
3	exp *diet/ or exp *diet therapy/ or *food intake/ or *eating/ or exp *dietary intake/ or exp feeding behavior/ or (intake or food* or diet* or nutrition* or eat*).ti,ab,kw. or exp exercise/ or exp

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	*kinesiotherapy/ or *fitness/ or exp *sport/ or physical activity/ or (activ* or sport* or exercis* or walk*).ti,ab,kw. or lifestyle modification.ti.
4	*prevention/ or "prevention and control"/ or primary prevention/ or pc.fs. or exp practice guideline/ or (guideline* or intervention* or advice* or recommendation* or prevent* or promot* or support*).ti,ab,kw.
5	exp clinical trial/ or exp controlled clinical trial/ or randomized controlled trial/ or clinical study/ or "clinical trial (topic)"/ or exp "randomized controlled trial (topic)"/ or case study/ or clinical study/ or cohort analysis/ or retrospective study/ or prospective study/ or exp comparative study/ or exp controlled study/ or experimental study/ or observational study/ or prevention study/ or validation study/ or "systematic review"/ or multicenter study/ or pilot study/ or (before adj10 (after or during)).ti,ab. or (trial or controlled).ti. or random*.ti,ab. or ((experiment* or quasi* or random* or control) adj3 (method* or study or trial or design*)).ti,ab,kw.
6	child/ not adult/
7	(animal/ not human/) or (exp experimental animal/ or animal experiment/ or animal model/ or exp rodent/ or editorial/ or letter/ or literature/ or (letter* or comment* or abstracts).ti.)
8	(1 and 2 and 3 and 4 and 5) not 6 not 7

Cochrane library:

ID Search

#1 MeSH descriptor: [Asia, Western] this term only

#2 MeSH descriptor: [Bangladesh] explode all trees

#3 MeSH descriptor: [Sri Lanka] explode all trees

#4 MeSH descriptor: [Nepal] explode all trees

#5 MeSH descriptor: [Bhutan] explode all trees

#6 MeSH descriptor: [India] explode all trees

#7 MeSH descriptor: [Pakistan] explode all trees

#8 South Asia* or Asian India* or Pakistan* or Bangladesh* or Sri Lanka* or Nepal* or Bhutan* or India*:ti,ab,kw (Word variations have been searched)

#9 MeSH descriptor: [Asia, Western] explode all trees

#10 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8

#11 MeSH descriptor: [Diabetes Mellitus] this term only

#12 MeSH descriptor: [Diabetes Mellitus, Type 2] explode all trees

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#13 MeSH descriptor: [Overweight] explode all trees

#14 diabet* or obes* or overweigh*:ti,ab,kw (Word variations have been searched)

#15 #11 or #12 or #13 or #14

#16 MeSH descriptor: [Diet] explode all trees

#17 MeSH descriptor: [Diet Therapy] explode all trees

#18 MeSH descriptor: [Eating] explode all trees

#19 MeSH descriptor: [Feeding Behavior] explode all trees

#20 intake or food* or diet* or nutrition* or eat*:ti,ab,kw (Word variations have been searched)

#21 MeSH descriptor: [Exercise] explode all trees

#22 MeSH descriptor: [Exercise Therapy] explode all trees

#23 MeSH descriptor: [Physical Fitness] explode all trees

#24 MeSH descriptor: [Sports] explode all trees

#25 MeSH descriptor: [Motor Activity] explode all trees

#26 MeSH descriptor: [Physical Education and Training] explode all trees

#27 activ* or sport* or exercis* or walk*:ti,ab,kw (Word variations have been searched)

#28 #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27

#29 MeSH descriptor: [Primary Prevention] explode all trees

#30 MeSH descriptor: [Guideline] explode all trees

#31 guideline* or intervention* or advice* or recommendation* or prevent* or promot* or support*:ti,ab,kw (Word variations have been searched)

#32 MeSH descriptor: [Health Planning Guidelines] explode all trees

#33 #29 or #30 or #31 or #32

#34 #10 and #15 and #28 and #33

Web of Science:

# 5	#4 AND #3 AND #2 AND #1 Indexes=SCI-EXPANDED, SSCI Timespan=All years
# 4	TITLE: (diabet* OR obes* OR overweight OR weight)

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	Indexes=SCI-EXPANDED, SSCI Timespan=All years
# 3	TOPIC: (guideline* OR intervention* OR advice* OR recommendation* OR prevent* OR promot* OR support*) Indexes=SCI-EXPANDED, SSCI Timespan=All years
# 2	TOPIC: (intake OR food* OR diet* OR nutrition* OR eat* OR activ* OR sport* OR exercis* OR walk*) Indexes=SCI-EXPANDED, SSCI Timespan=All years
# 1	TITLE: (South Asia* OR Asian India* OR Pakistan* OR Bangladesh* OR Sri Lanka* OR Nepal* OR Bhutan* OR India*) Indexes=SCI-EXPANDED, SSCI Timespan=All years

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ESM Tables (Must check the formatting of these tables – bold, footnotes etc once more)

ESM Table 1. Characteristics of excluded studies

Study ID/ year	Study design	Country	Ethnicity	Age (yrs)	% Male	Target group	Sample (n)	Duration*	Intervention	Reason for exclusion
Mayer-Davis (2004)[33]	RCT	USA	Asian American	⩾ 25	12	High risk for T2D	155	12	Diet, PA, weight reduction	Wide range Asian ethnicity
Snehalatha (2008)[34]	RCT	India	Indian	35-55	79	High risk for T2D	531	36	Diet, PA, medication	Secondary analysis / cohort study
Snehalatha (2009)[37]	RCT	India	Indian	35-55	79	High risk for T2D	437	36	Diet, PA, medication	Secondary analysis / cohort study
Ramachandran (2010)[37]	RCT, but arms combined	India	Indian	35-55	83	High risk for T2D	845	36	Diet, PA	Secondary analysis
Patel (2011)[37]	RCT	UK	South Asian	<55	-	High risk for T2D	50	2	Diet (low Glycemic Index components)	No results reported
Ram (2014)[38]	RCT, but arms combined	India	Indian	35-55	100	High risk for T2D	537	24	Diet, PA	Secondary analysis / cohort study

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Weber (2016)[39]	RCT	India	Indian	20-65	63	High risk for T2D	578	36	Diet, PA, medication	No identifiable subgroup without medication use
Willis (2016)[40]	Feasibility study	UK	Punjabi, Sikh and Gujarati Hindu	35-75	49	High risk for T2D	202	-	PA (walking)	No results reported
Patel (2017)[41]	RCT	US	Asian Indians	> 18	44	High risk for T2D	70	3+3	Diet, PA	Considered of weak quality, see Suppl. table 2
Wijesuriya (2017)[42]	RCT	Sri Lanka	Sri Lankan	6-40	48	Risk factors for T2D	4672	36	Diet, PA, weight education, stress reduction	No non-lifestyle intervention control group
Thankappan (2018)[32]	Cluster-RCT	India	Indian	30-60	47	High risk for T2D	1007	24	Diet, PA, weight maintenance, tobacco cessation, reducing alcohol, adequate sleep	Published after date of inclusion into IPD

* Duration in months, RCT: Randomised controlled study, PA: Physical activity,

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ESM Table 2. Quality assessment of potentially eligible studies

Study ID/year	Selection Bias	Design	Confounders	Blinding	Data Collection	Drop-Outs	Overall rating*	Included
IDPP-1 (2006)[12]	2	1	1	2	1	1	Strong	Yes
PAMH (2012)[18]	1	1	1	2	1	1	Strong	Yes
InnvaDiabDE-PLAN (2013)[17]	1	1	1	3	1	1	Moderate	Yes
DHIAAN (2013)[15]	2	1	1	2	1	2	Strong	Yes
Indian SMS Study (2013)[26]	1	1	1	2	1	1	Strong	Yes
PODOSA (2014)[16]	1	1	1	2	1	1	Strong	Yes
Patel 2017[41]	3	1	1	2	1	3	Weak	No

* The Quality Assessment Tool for Quantitative Studies[23] developed by the Effective Public Health Practice Project was used. Rating: 1= strong, 2 = moderate, 3 = weak. The quality assessment for DHIAAN was based on published paper for results after 12 months, but in the present paper we use 2 year data.

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ESM Table 3. Lost to follow-up by study duration

		Total	Intervention	Control
IDDP-1[12]	**Baseline**	253	120	133
	1 year	253	120	133
	Lost to follow-up (n)	0	0	0
	Lost to follow-up (%)	0	0	0
	2 year	253	120	133
	Lost to follow-up (n)	0	0	0
	Lost to follow-up (%)	0	0	0
	3 year	253	120	133
	Lost to follow-up (n)	0	0	0
	Lost to follow-up (%)	0	0	0
PAMH[18]	**Baseline**	139	85	54
	5 months	120	73	47
	Lost to follow-up (n)	19	12	7
	Lost to follow-up (%)	13.7	14.1	13.0
InnvaDiab-DEPLAN[17]	**Baseline**	180	92	88
	7 months	139	71	68
	Lost to follow-up (n)	41	21	20
	Lost to follow-up (%)	22.8	22.8	22.7
DHIAAN[15]	**Baseline**	536	283	253
	1 year	340	179	161
	Lost to follow-up (n)	190	101	89
	Lost to follow-up (%)	35.8	36.1	35.6
	2 year	324	167	157
	Lost to follow-up (n)	206	113	93
	Lost to follow-up (%)	38.9	40.4	37.2

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Indian SMS study[26]	**Baseline**	537	271	266
	1 year	494	250	244
	Lost to follow-up (n)	43	21	22
	Lost to follow-up (%)	8.0	7.7	8.3
	2 year	476	246	230
	Lost to follow-up (n)	61	25	36
	Lost to follow-up (%)	11.4	9.2	13.5
PODOSA[16]	**Baseline**	171	85	86
	1 year	169	84	85
	Lost to follow-up (n)	2	1	1
	Lost to follow-up (%)	1.2	1.2	1.2
	2 year	167	83	84
	Lost to follow-up (n)	4	2	2
	Lost to follow-up (%)	2.3	2.4	2.3
	3 year	167	84	83
	Lost to follow-up (n)	4	1	3
	Lost to follow-up (%)	2.3	1.2	3.5

Numbers are based on those randomized at inclusion

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ESM Table 4. Baseline participant characteristics

	N	Intervention, mean (SD)	N	Control, mean (SD)	Differences
IDDP-1[12]					
Weight (kg)	120	67.9 (10.19)	133	69.5 (10.42)	-1.6
Waist (cm)	120	88.9 (8.6)	133	89.7 (8.23)	-0.8
Body mass index (BMI)	120	25.7 (3.4)	133	26.3 (3.67)	-0.60
Fasting glucose (mmol/l)	120	5.4 (0.72)	133	5.5 (0.78)	-0.1
2-hr glucose (mmol/l)	120	8.5 (0.71)	133	8.6 (0.75)	-0.1
Age (years)	120	45.9 (5.85)	133	45.2 (5.64)	0.7
Women (%)	27	22.5	33	24.8	-2.3
Men (%)	93	77.5	100	75.2	2.3
PAMH[18]					2.20
Weight (kg)	85	83.7 (12.04)	54	83.7 (13.76)	0.00
Waist (cm)	85	97.7 (8.83)	54	98.6 (11.30)	-0.90
Body mass index (BMI)	85	27.08 (3.20)	54	27.2 (4.12)	-0.12
Fasting glucose (mmol/l)	84	5.2 (0.39)	53	5.2 (0.42)	0.00
2-hr glucose (mmol/l)	85	6.1 (1.59)	54	6.5 (1.72)	-0.40
Age (years)	84	35.6 (5.89)	54	39.2 (9.11)	-3.60
Men (%)	85	100	54	100	0
InnvaDiab-DEPLAN[17]					
Weight (kg)	92	72.6 (14.04)	88	75.25 (14.69)	-2.65
Waist (cm)	90	94.8 (13.33)	88	96.1 (11.38)	-1.30
Body mass index (BMI)	92	29.1 (5.70)	88	29.7 (5.70)	-0.60

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Fasting glucose (mmol/l)	92	5.2 (0.52)	87	5.1 (0.42)	0.10
2-hr glucose (mmol/l)	91	6.5(1.79)	85	6.3 (1.14)	0.20
Age (years))	92	40.1 (7.63)	88	41.3 (8.16)	-1.2
Women (%		100		100	0
DHIAAN[15]					
Weight (kg)	280	75.2 (13.60)	250	75.1 (13.91)	0.1
Waist (cm)	279	92.6 (10.73)	249	93.0 (11.07)	-0.40
Body mass index (BMI)	280	27.7 (4.03)	250	27.7 (4.23)	0.00
Fasting glucose (mmol/l)	282	5.3 (0.55)	252	5.3 (0.51)	0.00
2-hr glucose (mmol/l)	278	6.1 (1.65)	245	5.9 (1.69)	2.69
Age (years)	283	43.6 (10.97)	253	43.5 (9.70)	2.7
Women (%)	147	51.9	124	49.21	0.21
Men (%)	136	48.1	128	50.79	-2.69
Indian SMS study[26]					
Weight (kg)	271	72.3 (10.04)	266	71.8 (9.44)	0.5
Waist (cm)	271	92.5 (7.07)	266	92.6 (7.31)	-0.1
Body mass index (BMI)	271	25.8 (3.30)	266	25.8 (2.99)	0.00
Fasting glucose (mmol/l)	271	5.6 (0.53)	266	5.5 (0.55)	-0.1
2-hr glucose (mmol/l)	271	8.7 (0.78)	266	8.8 (0.85)	-0.1
Age (years)	271	45.9 (4.77)	266	46.1 (4.62)	-0.2
Men (%)	271	100	266	100	0
PODOSA[16]					
Weight (kg)	85	79.8 (16.23)	86	80.7 (14.98)	-0.90

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Waist (cm)	85	102.7 (11.15)	86	103.3 (11.01)	-0.60
Body mass index (BMI)	85	30.6 (5.02)	86	30.5 (4.60)	0.10
Fasting glucose (mmol/l)	85	5.8 (0.61)	86	5.8 (0.61)	0.00
2-hr glucose (mmol/l)	85	8.2 (1.63)	86	8.3 (1.50)	-0.10
Age (years)	85	52.6	86	52.2	-0.40
Women (%)	46	54.1	47	54.7	-0.60
Men (%)	39	45.9	39	45.4	0.50

Note: Data are n (%) or mean (SD) unless otherwise specified. Numbers are based on those randomized at inclusion with valid measurements on the respective variables.

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ESM Table 5. Effects of lifestyle interventions (mean difference) on secondary outcomes by subgroups

Outcome	Studies (N)	Participants, N Intervention/Contol	Intervention Mean (SD) Kg	Control Mean (SD) Kg	Summary Adjusted MD* (95% CI)	P**	I^2 (%)	P interaction***
Sex								
Fasting glucose (mmol/l)								
Men	5	495/466	5.6 (0.91)	5.7 (1.25)	-0.06 (-0.19, 0.08)	0.43	45	0.93
Women	4	232/217	5.3 (0.82)	5.4 (0.89)	-0.05 (-0.15, 0.05)	0.35	0	
2-hr glucose (mmol/l)								
Men	5	514/477	7.7 (2.51)	8.4 (3.21)	-0.47 (-0.85, -0.09)	**0.02**	51	0.36
Women	4	229/207	6.7 (2.15)	7.2 (2.65)	-0.22 (-0.58, 0.13)	0.22	18	
Weight (kg)								
Men	5	526/495	74.9 (12.56)	75.1 (12.14)	-1.05 (-1.98 -0.12)	**0.03**	81	0.26
Women	4	235/222	71.2 (13.85)	71.9 (12.83)	-0.43 (-0.97, 0.11)	0.12	0	
Waist (cm)								
Men	5	519/486	93.7 (9.35)	94.3 (9.21)	-1.22 (-2.49, 0.04)	0.06	79	0.78
Women	4	235/221	93.8 (11.83)	94.7 (10.82)	-1.00 (-1.92, -0.08)	**0.03**	0	
BMI groups								
Fasting glucose (mmol/l)								
≥ 27.5 kg/m²	6	359/355	5.4 (0.85)	5.5 (1.05)	-0.03 (-0.17, 0.12)	0.19	33	0.79
<27.5 kg/m²	6	368/329	5.6 (0.92)	5.8 (1.24)	-0.03 (-0.11, 0.05)	0.48	0	
2-hr glucose (mmol/l)								
≥ 27.5 kg/m²	6	358/349	6.8 (2.28)	7.4 (2.9)	-0.22 (-0.70, 0.25)	0.35	52	0.75

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<27.5 kg/m²	6	385/336	7.9 (2.49)	8.7 (3.15)	-0.31 (-0.54, -0.08)	**0.008**	1	
Weight (kg)								
≥ 27.5 kg/m²	6	374/372	79.7 (14.40)	79.7 (13.25)	-0.96 (-1.71 -0.21)	**0.01**	46	0.53
<27.5 kg/m²	6	387/346	68.0 (8.26)	68.2 (8.02)	-0.66 (-1.24, -0.08)	**0.02**	56	
Waist (cm)								
≥ 27.5 kg/m²	6	370/366	98.5 (11.17)	98.6 (10.46)	-1.13 (-2.42, 0.16)	0.09	54	0.57
<27.5 kg/m²	6	384/342	89.1 (6.35)	90.0 (6.42)	-0.95 (-1.84, -0.06)	**0.04**	53	
Age								
Fasting glucose (mmol/l)								
>44 years	6	399/382	5.6 (0.86)	5.7 (1.05)	-0.08 (-0.18, 0.02)	0.14	0	0.38
≤ 44 years	6	328/302	5.4 (0.92)	5.5 (1.26)	-0.00 (-0.14, 0.14)	0.99	46	
2-hr glucose (mmol/l)								
>44 years	6	405/389	7.6 (2.41)	8.1 (3.02)	-0.39 (-0.78, 0.00)	0.05	47	0.66
≤ 44 years	6	338/296	7.1 (2.47)	7.9 (3.19)	-0.27 (-0.60, 0.05)	0.10	29	
Weight (kg)								
>44 years	6	415/402	72.5 (12.36)	73.2 (11.98)	-0.79 (-1.45, -0.13)	**0.02**	57	0.61
≤ 44 years	6	346/316	75.2 (13.76)	75.3 (12.93)	-0.52 (-1.34, 0.31)	0.22	66	
Waist (cm)								
>44 years	6	413/396	94.3 (9.79)	94.7 (9.40)	-0.55 (-1.49, 0.40)	0.26	46	0.34
≤ 44 years	6	341/312	93.0 (10.60)	94.1 (10.14)	-1.36 (-2.73, 0.01)	0.05	71	
Study duration								

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Fasting glucose (mmol/l)								
5-7 months	2	142/114	5.2 (0.53)	5.2 (0.48)	-0.04 (-0.14, 0.06)	0.44	0	0.81
2-3 years	4	585/570	5.6 (0.95)	5.7 (1.23)	-0.06 (-0.23, 0.09)	0.41	56	
2-hr glucose (mmol/l)								
5-7 months	2	138/106	5.7 (1.50)	6.0 (1.59)	-0.12 (-0.53, 0.28)	0.55	31	0.22
2-3 years	4	605/579	7.8 (2.46)	8.4 (3.16)	-0.47 (-0.86, -0.09)	**0.01**	56	
Weight (kg)								
5-7 months	2	144/115	77.6 (13.87)	77.9 (14.17)	-1.22 (-2.23, -0.18)	**0.02**	64	0.39
2-3 years	4	617/603	72.8 (12.73)	73.4 (11.97)	-0.54 (-1.23, 0.14)	0.12	71	
Waist (cm)								
5-7 months	2	143/114	95.5 (11.54)	97.2 (10.57)	-2.17 (-4.57, 0.22)	0.08	84	0.24
2-3 years	4	611/594	93.3 (9.80)	93.9 (9.48)	-0.66 (-1.51, 0.18)	0.12	50	
Study region								
Fasting glucose (mmol/l)								
Europe	4	388/347	5.2 (0.73)	5.3 (0.85)	-0.05 (-0.13, 0.03)	0.25	0	0.71
India	2	339/337	5.8 (0.96)	6.0 (1.32)	-0.13 (-0.59, 0.32)	0.56	83	
2-hr glucose (mmol/l)								
Europe	4	378/329	6.1 (1.95)	6.6 (2.24)	-0.22 (-0.46, 0.01)	**0.07**	2	0.40
India	2	365/356	8.7 (2.24)	9.4 (3.18)	-0.69 (-1.74, 0.36)	0.20	84	
Weight (kg)								
Europe	4	395/355	76.6 (14.65)	77.0 (13.90)	-1.10 (-1.66, -0.54)	**0.0001**	42	**0.02**
India	2	366/363	70.6 (10.28)	71.3 (10.08)	-0.08 (-0.75, 0.58)	0.81	50	
Waist (cm)								

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Europe	4	394/354	95.8 (11.43)	96.9 (10.92)	-1.59 (-2.94, -0.27)	**0.02**	75	0.09
India	2	360/354	91.4 (8.01)	92.0 (7.64)	-0.26 (-1.00, 0.47)	0.46	0	

*Model based on pooled data with last estimate (Podosa and IDDP =3 years, DHIAAN and Indian SMS Study = 2 years, InnvaDiab = 7 months and PAMH= 5 months), adjusted for age and baseline values for outcome variable. ** P values for mean difference, p values < 0.05 in bold. *** P values for interaction term for subgroup analyses, p values < 0.05 in bold

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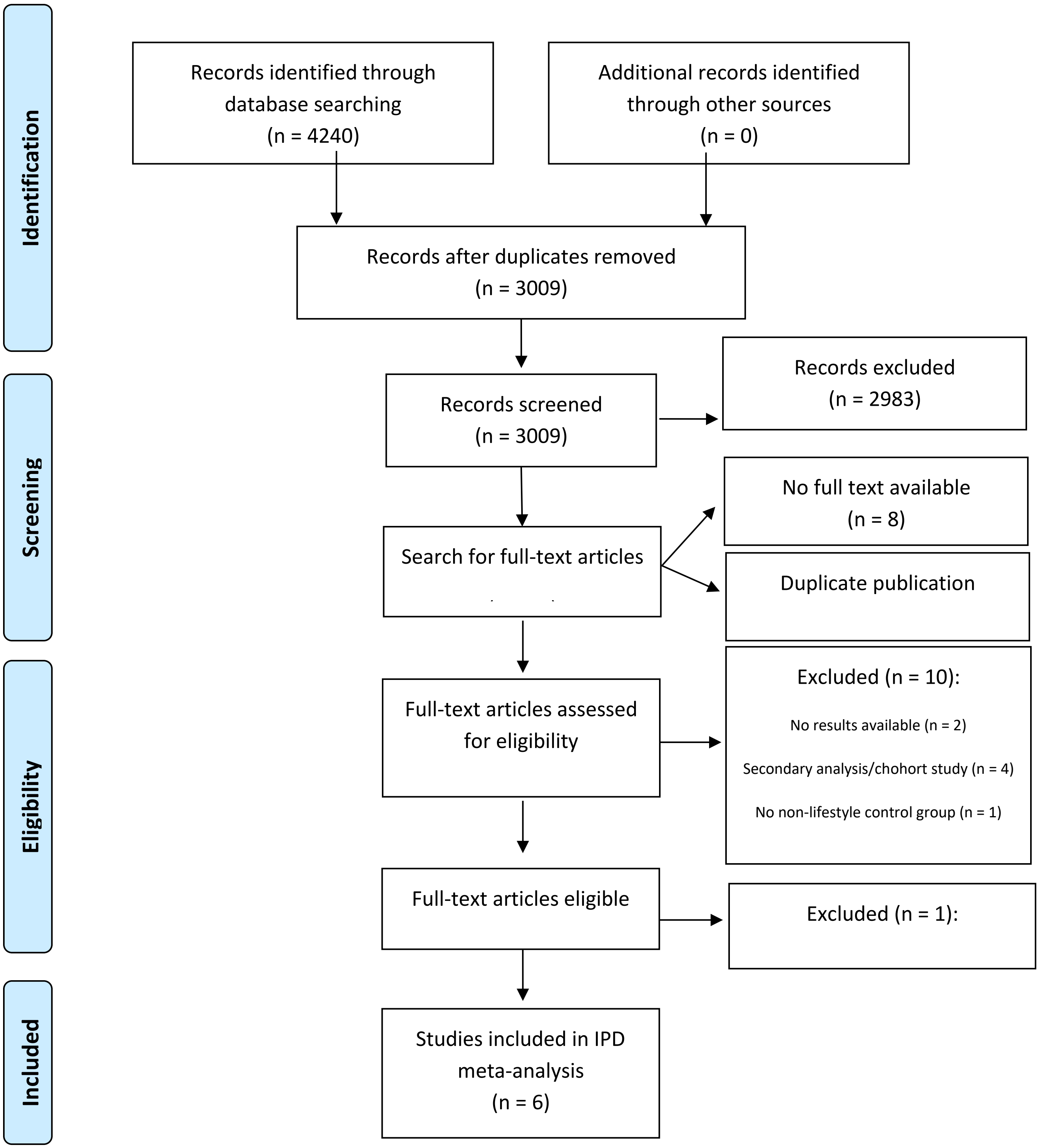
ESM Figure 1. Flow Diagram



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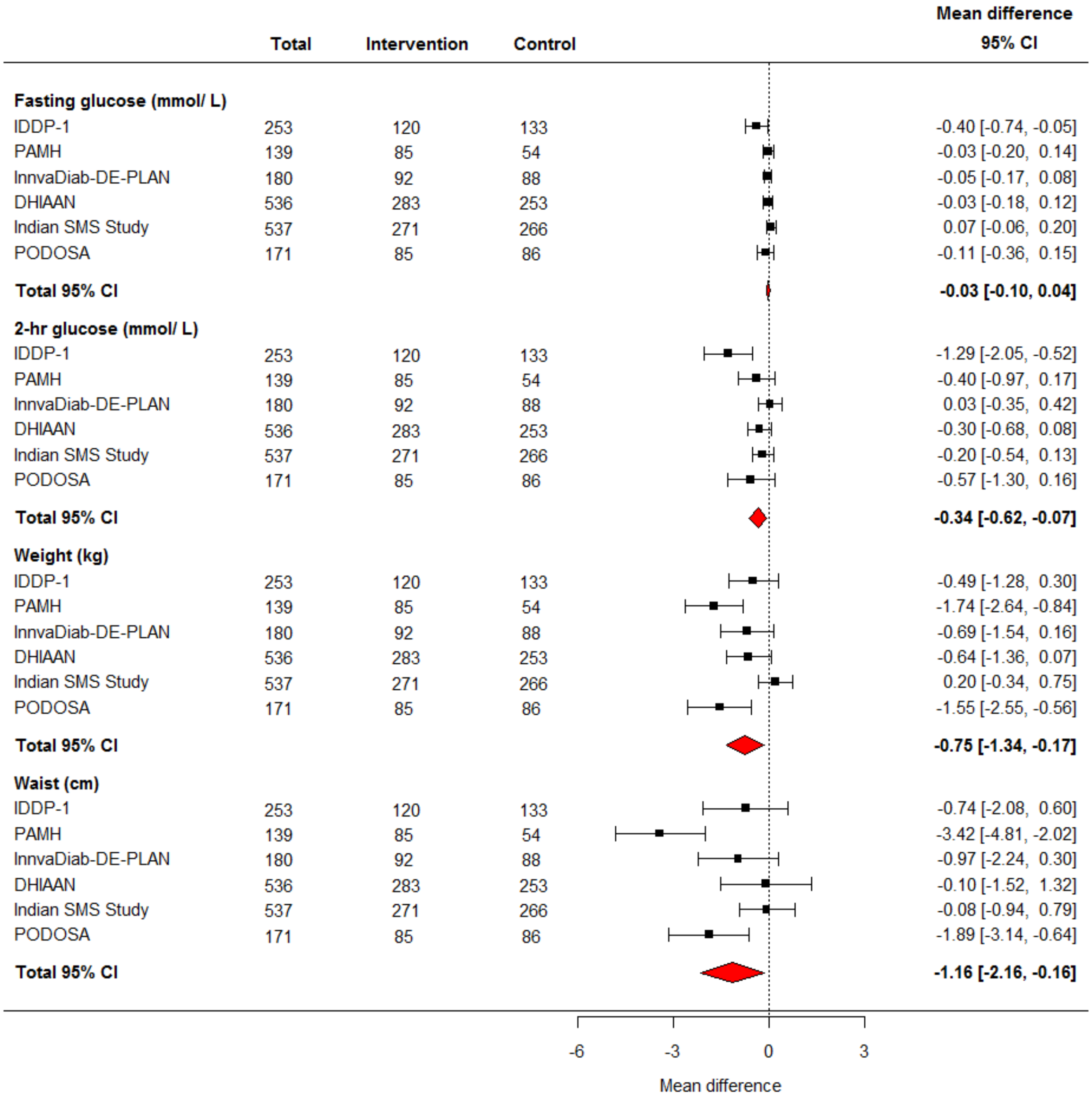

ESM Figure 2. Effects (mean difference) for secondary continuous outcomes

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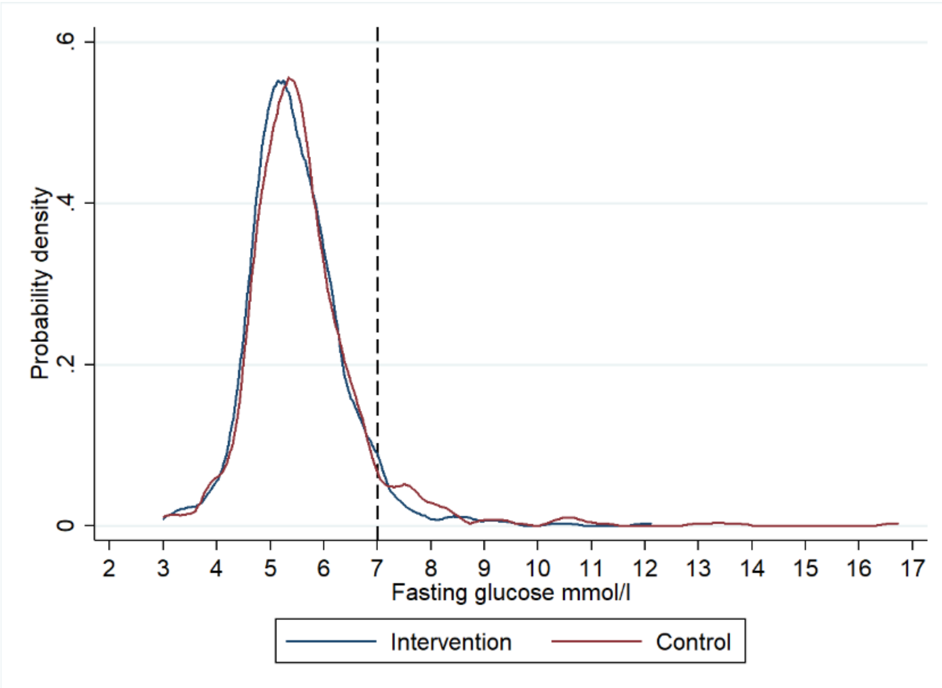
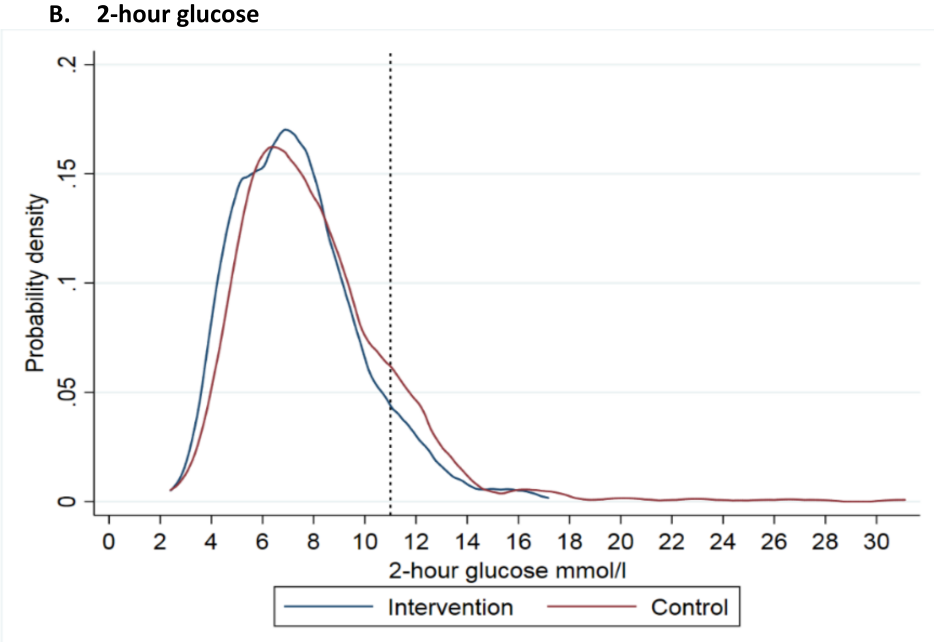
A. Fasting Glucose



B. 2-hour glucose



ESM Figure 3. Distribution curves at last follow-up for all studies merged