Effect of lifestyle interventions on cardiovascular risk factors among adults without impaired glucose tolerance or diabetes: A systematic review and meta-analysis

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Abstract

Structured lifestyle interventions can reduce diabetes incidence and cardiovascular disease (CVD) risk among persons with impaired glucose tolerance (IGT), but it is unclear whether they should be implemented among persons without IGT. We conducted a systematic review and meta-analyses to assess the effectiveness of lifestyle interventions on CVD risk among adults without IGT or diabetes. We systematically searched MEDLINE, EMBASE, CINAHL, Web of Science, the Cochrane Library, and PsychInfo databases, from inception to May 4, 2016. We selected randomized controlled trials of lifestyle interventions, involving physical activity (PA), dietary (D), or combined strategies (PA+D) with follow-up duration ≥12 months. We excluded all studies that included individuals with IGT, confirmed by 2-hours oral glucose tolerance test (75g), but included all other studies recruiting populations with different glycemic levels. We stratified studies by baseline glycemic levels: (1) low-range group with mean fasting plasma glucose (FPG) <5.5mmol/L or glycated hemoglobin (A1C) <5.5%, and (2) high-range group with FPG ≥5.5mmol/L or A1C ≥5.5%, and synthesized data using random-effects models. Primary outcomes in this review included systolic blood pressure (SBP), diastolic blood pressure (DBP), total cholesterol (TC), low density lipoprotein cholesterol (LDL-C), high density lipoprotein cholesterol (HDL-C), and triglycerides (TG). Totally 79 studies met inclusion criteria. Compared to usual care (UC), lifestyle...
interventions achieved significant improvements in SBP (-2.16 mmHg [95% CI, -2.93, -1.39]), DBP (-1.83 mmHg [-2.34, -1.31]), TC (-0.10 mmol/L [-0.15, -0.05]), LDL-C (-0.09 mmol/L [-0.13, -0.04]), HDL-C (0.03 mmol/L [0.01, 0.04]), and TG (-0.08 mmol/L [-0.14, -0.03]). Similar effects were observed among both low- and high-range study groups except for TC and TG. Similar effects also appeared in SBP and DBP categories regardless of follow-up duration. PA+D interventions had larger improvement effects on CVD risk factors than PA alone interventions. In adults without IGT or diabetes, lifestyle interventions resulted in significant improvements in SBP, DBP, TC, LDL-C, HDL-C, and TG, and might further reduce CVD risk.

Introduction

Cardiovascular disease (CVD) is the number one killer globally.[1] CVD is also the major cause of morbidity and mortality among persons with diabetes, and the largest contributor to health care costs associated with diabetes.[2,3] On the other hand, CVD and diabetes share similar risk factors such as unhealthy diet, physical inactivity, and obesity.[2–4] Previous studies have demonstrated that structured lifestyle interventions incorporating physical activity, diet, and behavior change strategies could prevent or delay type 2 diabetes incidence and reduce CVD risk factors.[5–7] However, these major prevention trials focused on populations with impaired glucose tolerance (IGT).[5–7] Although individuals with IGT are the priority target population because they lie at the higher end of the diabetes risk spectrum, populations without IGT but with other CVD risk factors may outnumber those with high diabetes risk and have the same urgent needs for risk reduction, as many RCT studies have indicated.[8–14] According to the American Diabetes Association’s (ADA) definitions of pre-diabetes (which includes impaired fasting glucose (IFG): 100–125 mg/dL), about 60% of US individuals with pre-diabetes do not have IGT,[15] and according to the World Health Organization’s (WHO) definition of intermediate hyperglycemia (measured by fasting plasma glucose (FPG): 110–139 mg/dL), about 70% of individuals with this condition do not have IGT.[16] Whether lifestyle interventions should be applied more broadly to the population at lower risk (i.e. those below the IGT threshold) to reduce CVD risk needs to be examined.

According to an American Heart Association (AHA) Special Report,[17] cardiovascular health is defined by 7 metrics, including health behaviors and health indicators as follows: smoking status, body mass index (BMI), physical activity (PA) levels, healthy diet scores, total cholesterol (TC), blood pressure (BP) level, and fasting plasma glucose level. To achieve the AHA ideal cardiovascular health promotion goal, each indicator must fall into certain ranges (e.g., FPG < 100 mg/dL). This definition of cardiovascular health addresses health behaviors and health indicators related to both CVD and diabetes, and thus offer guidance for how to achieve improvements in preventing both CVD and diabetes at the same time.

Evidence regarding the effects of lifestyle intervention on CVD risk reduction has previously been systematically synthesized by examining 6 of the 7 CVD health indicators mentioned above, especially by examining the different stratum of BMI (e.g., moderate weight loss will reduce both diabetes and CVD risk among overweight or obese populations[5–7]), as indicated by the 2013 AHA/ACC Guideline on Lifestyle Management to Reduce Cardiovascular Risk.[18] However, how this evidence is aligned with the stratification of different glucose levels is still unclear. Lack of this information may prevent public health practitioners from fully understanding the role lifestyle interventions can play in reducing both diabetes and CVD risk.
among populations with varying risk levels. In contrast, a synthesis of evidence on the impact of lifestyle interventions among populations with different risk levels may help to inform decisions regarding the allocation of finite public health resources.

We conducted a systematic review to assess the aggregated impact of lifestyle interventions on glucose regulation and CVD risk factors among adults (age ≥18 years) without IGT or diabetes. By conducting this review, we intend to answer the following research question: can lifestyle interventions similar to those found efficacious among populations with IGT achieve the same magnitude of improvement in CVD risk reduction among populations with lower diabetes risk? We also aimed to examine whether lifestyle interventions focused on diet, PA or their combination have varying impact on CVD risk reduction. To understand how to reach the comprehensive goal of preventing both CVD and diabetes, we also examined how the lifestyle interventional effect on CVD risk reduction is related to the effect sizes of glucose improvement and weight loss.

Materials and methods
Search strategy and selection criteria
We followed Cochrane Collaboration standards for a meta-analysis of randomized control trial (RCT) studies to develop our protocol.[19] We systemically searched MEDLINE, EMBASE, CINAHL, Web of Science, the Cochrane Library, and PsycINFO databases, from inception to May 4, 2016. Medical Subject Headings, text words, and search strategies are presented in our online-only supplements (S1 File). We examined reference lists of all included studies and relevant reviews for additional studies. We directly contacted authors to clarify data as needed.

We selected RCTs published in any language that examined lifestyle strategies involving PA and/or dietary (D) interventions, among adults (≥18 years) and with glycemic indicators and CVD risk factors reported as intervention outcomes (e.g., systolic blood pressure (SBP), diastolic blood pressure (DBP), TC, low density lipoprotein cholesterol (LDL-C), high density lipoprotein cholesterol (HDL-C), or triglycerides (TG)). Included studies investigated persons without IGT or diabetes. We excluded all studies that included individuals with IGT, confirmed by 2-hours oral glucose tolerance test (75g), but included all other studies recruiting populations with different glycemic levels. However, to examine whether there was heterogeneity of effect by baseline glycemia, we grouped all studies as: (1) low range glycemia group with mean fasting plasma glucose (FPG) < 5.5mmol/L or mean glycated hemoglobin (A1C) < 5.5% and (2) high range group with mean FPG ≥5.5mmol/L or mean A1C ≥5.5%. Data from the low and high range glycemic groups were analyzed separately. We only included interventions with a follow-up interval of at least 12 months.

Study selection and data extraction
Two reviewers independently reviewed each article title and abstract for inclusion. If any disagreement occurred between two reviewers, a third reviewed the item and consensus was reached through discussions.

We extracted data regarding demographic and intervention characteristics. Primary outcomes included SBP, DBP, TC, LDL-C, HDL-C, and TG. In our review, all interventions were classified as PA alone, D alone, or combined interventions (PA+D). PA interventions included any strategy used to promote physical activity levels using counseling, exercise prescription, and/or a supervised or unsupervised exercise program. D interventions included any strategy used to reduce or control calorie intake, e.g., very low-calorie diet (<800 kcal/d) or low-calorie diet (800 to 1500 kcal/d). Studies using combined PA and D strategies usually also employed
behavioral modification strategies, including counseling, education, cognitive-behavioral therapy, or social support, as an intervention component.

Statistical analysis and quality assessment

We assessed study quality by examining potential selection, attrition, and detection bias.[19] We did not exclude any study that was considered poor quality (e.g., studies with attrition ≥30%). However, we conducted a sensitivity analysis to compare pooled effects between studies with potentially significant bias and those without. For example, for those studies with attrition ≥30%, their data were not used in our primary meta-analyses, but were used in our sensitivity analyses.

Among studies with similar intervention and comparison groups reporting a similar outcome of interest, we conducted meta-analyses to determine pooled effects. We calculated the mean difference between baseline and follow-up measures for the intervention (I) and comparison (C) groups (delta I and delta C) and the standard error of each difference. We used three strategies to estimate pooled effects: (1) stratified by baseline glucose levels (low range vs. high range); (2) stratified by the length of follow-up (12 months vs. 13–23 months vs. ≥24 months); and (3) stratified by type of interventions (PA vs. D vs. PA+D).

We used DerSimonian and Laird random-effects models[20] to determine pooled effects. Effect size was defined by the mean difference between delta I and delta C divided by the standard deviation of the mean. We used meta-regression to determine whether various study-level characteristics (mean age, follow-up interval, duration of the intervention, number of intervention contacts, attrition, and year of publication) affected the between-group differences in SBP, DBP, TC, LDL-C, HDL-C, and TG, and we examined interaction terms for all models. We also used meta-regression analyses to examine the relationship between interventional effects on CVD risk reduction and interventional effects on diabetes risk reduction measured by the effect sizes of glucose improvement and weight loss. The meta-regression was conducted using SPSS (version 20.0, Armonk, NY: IBM Corp.). We used the chi-squared test to examine heterogeneity, and we used Cochrane Review Manager software (version 5.1; Copenhagen, Denmark) to calculate pooled effects.

If a comparison group in a study used a similar approach as the intervention group did, but only differed in dose, intensity, or frequency (e.g., diet plan A vs. diet plan B; or swimming vs. walking), we analyzed the effects of treatment in a single arm model to determine within-group changes (between post-intervention and pre-intervention in one arm) for both intervention and comparison group. These effects were also estimated by using the DerSimonian and Laird random-effect model. We did not, however, conduct any sensitivity analysis for these studies. Because this paper focused on the net lifestyle intervention effect (any lifestyle intervention vs. no intervention [e.g., usual care (UC)]), pooled effects from our single arm model are not reported in our results section, but are presented as an online supplementary table (Table C in S1 File).

Results

Seventy-nine studies[10,11,13,14, 21–95] and 30 companion publications[9,96–124] encompassing 15618 participants (Table 1: range, 20 to 1089) fulfilled the inclusion criteria (Fig 1). Follow-up time ranged from 12 to 54 months. The mean age of the participants was 50.6 years (range, 30.2 to 70.4 year), and mean BMI was 30.5 kg/m$^2$ (range, 23.3 to 38.7 kg/m$^2$). Mean baseline SBP, DBP, TC, LDL-C, HDL-C, and TG were 127.5 mmHg, 79.2 mmHg, 5.4 mmol/L, 3.3 mmol/L, 1.3 mmol/L, and 1.5 mmol/L, respectively. More studies took place in community settings than in clinics (58 vs. 21). Sampling methods varied, but most participants were
| Citation | Sample size | Length of follow-up (months) | Age at BL (years) | Sex (% female) | Setting/Region | Race/ethnicity | BMI at BL (kg/m²) [mean (SD)] | SBP/DBP at BL (mmHg) [mean (SD)] | TC at BL (mmol/L) [mean (SD)] | LDL/HDL at BL (mmol/L) [mean (SD)] | TG at BL (mmol/L) [mean (SD)] | Inclusion criteria | Sampling method | Attrition (%) |
|----------|-------------|-----------------------------|------------------|----------------|----------------|---------------|-----------------------------|-----------------------------|-----------------------------|-----------------------------|-----------------------------|-----------------|----------------|--------------|
| Ackermann et al. 2008 | 92 | 12 | 58.3 (10.1) | 55.4 | Community | Indianapolis IN | 81.5% White, 12.0% Black | 31.4 (4.9) | 132.5 (16.5) 81.5 (9.1) | 4.9 (1.0) | NR | NR | People with ADA risk score ≥10 and casual capillary blood glucose (CCBG) of 110–188 mg/dL | Recruited from YMCA by community-based screening | 32.6 |
| Almeida et al. 2011 | 53 | 12 | 18.9 | 31.4 (4.9) | 132.5 | 81.5 (9.1) | 4.9 (1.0) | 2.8 (0.8) | NR | NR | 1.5 (0.8) | Aged: 20–39yrs, without hypothyroidism, hypertensive disease, obesity, cancer, anemia, or contraindicated drug use, or pregnancy | Recruited from a community-based screening program | 20.8 |
| Anderson et al. 2014 | 329 | 12 | 60.5 (6.8) | 26.0 | Community | Scotland UK | 99.0% White | 30.7 (4.2) | 142.5 (17.4) 84 (10.0) | 5.1 (1.2) | 3.0 (1.1) | 3.0 (1.1) | BMI ≥25 kg/m²; with polypctomy for adenoma, without pregnancy, DM | Recruited from a community-based screening program | 7.3 |
| Arguin et al. 2012 | 25 | 12 | 60.5 (6.0) | 100.0 | Community | Sherbrooke QC Canada | 79.6 (10.7) | 26.5 (5.0) | 124.5 (15.0) NR | 5.9 (1.1) | NR | NR | Obese people (BMI: 30–45 kg/m²) without DM and CVD | Recruited from community screenings and TV ads | 12.0 |
| Bazzano et al. 2014 | 148 | 12 | 46.8 (10.1) | 88.5 | Community | New Orleans LA | 45.3% White, 51.4% Black | 30.4 (4.2) | 122.6 (13.3) 78.4 (8.7) | 5.2 (1.1) | 3.2 (1.0) | 1.9 (0.3) | Obese, hyperinsulinemic persons aged between 20 and 60yrs, insulin ≥12 μU/mL without DM | Recruited from a community-based screening program | 17.8 |
| Bo et al. 2007/2009 | 375 | 48 | 50.7 (5.7) | 58.2 | Community | Asni Italy | 29.7 (4.4) | 142.1 (14.7) 88.0 (9.2) | 5.9 (1.1) | NR | NR | People with MetS defined by FPG>110 mg/dL without DM and CVD | Recruited from a community-based screening | 10.7 |
| Brinkworth et al. 2004 | 58 | 12 | 50.2 (NR) | 77.6 | Community | Adelaide Australia | 340 (NR) | 132.0 (13.9) 75.1 (10.7) | 5.6 (0.9) | 3.8 (0.9) | 1.9 (0.7) | Obese, hyperinsulinemic persons aged between 20 and 60yrs, insulin ≥12 μU/mL without DM | Recruited from a community-based screening program | 25.9 |
| Burke et al. 2007 & 2008 | 340 | 12 | 45.3 (12.9) | 59.7 | Community | Amsterdam The Netherlands | 12.5 (5.0) | 124.5 | 15.0 | NR | NR | 1.2 (0.4) | Aged: 18–70yrs, with bimodal hypertension, a LDL-C level >79th percentile | Recruited from the national cascade screening program | 7.4 |
| Buttarhar et al. 2005/2010 | 36 | 12 | 57.5 (6.9) | 55.6 | Community | Inverloch Victoria Australia | 20.9 (3.9) | 191.0 (25.9) 91.6 (11.0) | 5.8 (1.0) | NR | NR | Patients with IFG (FPG>100–125 mg/dL), aged >40–69yrs; BMI>25 kg/m², and without DM | Recruited from a community-based screening program | 12.0 |
| Chirinos 2016 | 120 | 12 | 51.7 (8.4) | 55.8 | Community | Coral Gables FL | 84.0% Hispanic, 10.9% Black | 125.2 (16.6) 79.3 (9.5) | 5.5 (1.0) | 3.3 (0.9) | 1.4 (0.4) | Aged: 30–70yrs, obese adults with WC ≥102 cm for males, 88 cm for females, FPG ≥100 mg/dL, HDL-C <40 mg/dL for males, <50 mg/dL for females, IFG ≥100 mg/dL | Recruited from low-income community clinics | 22.5 |
| Choo et al. 2014 | 110 | 12 | 43.1 (9.0) | 100.0 | Community | Seoul South Korea | 28.5 (3.8) | 116.5 (13.1) NR | 5.5 (1.0) | 3.3 (0.9) | 1.4 (0.4) | Aged: 18–65yrs, elevated waist circumference ≥85cm, abdominal obesity without DM and CVD | Recruited via poster, leaflet, telephone, and ads | 55.5 |
| Clifton et al. 2008 | 119 | 12 | 49.0 (9.0) | 55.6 | Community | Adelaide Australia | 32.8 (3.5) | 134.7 (13.9) 73.0 (10.1) | 6.3 (0.8) | NR | NR | Women aged: 20–65yrs, BMI ≥27–40 kg/m², without DM, or renal or liver disease | Recruited from public ads and screened | 33.6 |
| Coon et al. 1989 | 94 | 12 | 59.3 (9.6) | 46.0 | Community | San Antonio TX | 64.0% White, 17.0% Black, 18.0% Hispanic | 30.8 (4.9) | 143.0 (17.0) 83.0 (10.0) | 5.0 (1.0) | 2.9 (0.9) | 1.4 (0.4) | Aged ≥64yrs, without DM, but with pre-DM by ADA defined IFG (FPG 100–125 mg/dL) | Recruited from a pre-DM education class | 31.0 |
| Coop et al. 1991 | 20 | 12 | 59.5 (7.5) | 0.0 | Community | Baltimore MO | 29.0 (3.0) | 143.0 (17.0) 83.0 (10.0) | 5.0 (1.0) | 2.9 (0.9) | 1.4 (0.4) | Aged ≥64yrs, healthy persons without DM | Recruited by ads | 0.0 |
| Citation | Sample site | Length of follow-up (months) | Age at BL (years) | Sex (% female) | Setting: Race/ethnicity | BMI at BL (kg/m²) [mean (SD)] | SBPI/DBP at BL (mmHg) [mean (SD)] | TC at BL (mmol/L) [mean (SD)] | LDL/HDL at BL (mmol/L) [mean (SD)] | TG at BL (mmol/L) [mean (SD)] | Inclusion criteria | Sampling method | Attrition (%) |
|----------|-------------|-----------------------------|------------------|----------------|-------------------------|-------------------------------|-------------------------------|-------------------------------|----------------------------------|-------------------------------|-----------------|----------------|-------------|
| Cox et al 2006 & 2008 & 2010 | 116 | 12 | 55.5 (4.7) | 100.0 | Community | 26.4 (3.3) | NR | 5.2 (0.7) | 3.2 (0.7) | 1.5 (0.3) | 1.1 (0.5) | Aged: 50-74yrs; BMI=34 kg/m²; non-smoker, with sedentary lifestyle, without DM | Recruited by ads. | 25.9 |
| Otschurua et al 1999 & 2001 | 100 | 24 | 45.7 (10.6) | 79.0 | Citrus Ulm Germany | 33.4 (3.6) | 139.5 (14.6) | 82.5 (9.0) | 5.9 (1.0) | 1.3 (0.4) | 2.2 (1.3) | Aged: 18-69yrs, BMI between 25 and 40 kg/m² without endocrine disorders | Recruited by referring to the district clinic | 27.0 |
| Donnelly et al 2000 | 22 | 18 | 51.5 (8.5) | 100.0 | Community | 31.2 (4.0) | 133.0 (14.6) | 80.5 (9.2) | 4.9 (1.1) | 1.1 (0.3) | NR | BMI>05 kg/m², low aerobic capacity, at risk for continued weight gain | NR | 0.0 |
| Esposito et al 2003 | 120 | 24 | 34.6 (5.0) | 100.0 | Clinic Naples Italy | 34.9 (2.4) | 123.5 (9.2) | 85.0 (4.8) | 5.1 (0.6) | 1.2 (0.3) | 1.6 (0.5) | Obese premenopausal women, aged: 20-49yrs without DM, IGT (HDL=0.9-1.0 mmol/L), CAD, pregnancy, OGTT confirmed | Recruited from an outpatient dept | 6.7 |
| Esposito et al 2004a | 110 | 24 | 43.3 (5.0) | 0.0 | Clinic Naples Italy | 36.7 (2.4) | 127.5 (7.6) | 85.5 (3.9) | 5.5 (0.8) | 1.0 (0.3) | 1.9 (0.6) | Obese men with erectile dysfunction, aged: 35-55yrs; without DM and IGT, OGTT confirmed | Recruited from an outpatient department list | 5.5 |
| Esposito et al 2004b | 180 | 24 | 43.9 (6.2) | 45.0 | Clinic Naples Italy | 28.0 (3.3) | 130.0 (9.5) | 85.5 (6.5) | 5.1 (0.9) | 1.1 (0.2) | 1.9 (0.6) | Sedentary people with MetS, FPG=110 mg/dL | Recruited from a screening program | 8.9 |
| Fatouros et al 2005 | 50 | 12 | 70.4 (3.8) | 0.0 | Community | 29.5 (3.3) | NR | NR | NR | NR | Inactive d men, non-smoker, without DM, FPG<7 mmol/L | Recruited from a volunteer database in local community | 0.0 |
| Fernandez et al 2012 | 40 | 12 | 40.9 (13.5) | 67.5 | Community | 31.8 (2.4) | 124.8 (17.6) | 78.5 (12.6) | 5.2 (0.9) | 3.1 (0.7) | 1.4 (0.5) | Aged: 18-69yrs; BMI=28-35 kg/m², without DM and pregnancy | Recruited from a clinic trial | 60.0 |
| Ferrara et al 2012 | 188 | 24 | 56.4 (9.5) | 47.9 | Clinic | 29.2 (4.5) | 134.1 (16.0) | 84.4 (10.6) | 5.1 (0.9) | 3.2 (0.9) | 1.3 (0.3) | People with HT | Recruited from an outpatient clinic | 0.0 |
| Fischer et al 2016 | 163 | 12 | 46.4 (11.5) | 75.8 | Clinic Denver CO | NR | 118.8 (14.1) | NR | NR | NR | NR | Patients aged: 18yrs, with A1C: 5.7–6.4%, BMI: 25–50 kg/m², without DM | Recruited from health centers | 5.7 |
| Fisher et al 2012 | 97 | 12 | Range: 21–46 | 100.0 | Community | 28.0 (1.0) | NR | NR | NR | NR | Sedentary aged 18yrs, with A1C: 5.7–6.4%, BMI: 25–50 kg/m², without DM | Recruited from a previous parent study | 0.0 |
| Fogelholm et al 2000 | 82 | 24 | Range: 30–45 | 100.0 | Community | 34.0 (3.6) | 119.0 (10.0) | 78.0 (7.6) | 5.0 (0.9) | 1.2 (0.2) | 1.3 (0.5) | Aged: 30-45yrs; BMI=30-45 kg/m², physical inactive | Recruited by ads | 9.8 |
| Fonda et al 2009 | 297 | 12 | 46.0 (9.4) | 15.5 | Community | 28.8 (5.0) | 122.1 (15.2) | 79.5 (9.0) | 5.6 (1.0) | 1.7 (1.0) | 1.2 (0.3) | People with moderate risk of CVD, without DM and pregnancy | Recruited from a screening program | 14.8 |
| Frank et al 2005 | 173 | 12 | 60.7 (8.7) | 100.0 | Community | 30.4 (3.9) | NR | NR | NR | NR | 1.4 (0.6) | Postmenopausal women, aged: 50-74yrs, sedentary at baseline BMI>25 kg/m², without DM, non smoker | Recruited through a combination of mailings and media placements | 1.7 |
| Groncavà et al 2008 & 2010 | 816 | 12 | 46.6 (9.2) | 0.0 | Community | 28.5 (3.3) | 142.9 (15.3) | 88.8 (6.9) | NR | 1.1 (0.2) | NR | Male construction workers with increased risk of CVD | Recruited from Periodical Health Screening | 27.6 |
| Heshka et al 2003 | 423 | 24 | 44.5 (10.0) | 84.6 | Clinic | 33.7 (3.6) | 122.0 (13.0) | 79.0 (8.5) | 5.5 (1.0) | 1.3 (0.3) | 1.7 (0.5) | Aged: 18-65yrs; BMI=27–40 kg/m², with FPG<7.8 mmol/L | Recruited from existing clinic records, or by ads | 27.0 |
| Imayama et al 2013 | 439 | 12 | 58.0 (5.0) | 100.0 | Community | 30.9 (4.1) | NR | NR | NR | NR | Aged: 50-75yrs; BMI=25 kg/m²; <100 min/wk PA; postmenopausal; without DM, FPG<106 mg/dL | Recruited from mass mailing ads | 9.1 |
| Juul et al 2016 | 127 | 12 | 68.6 | Community | 133.0 (14.1) | 82.5 (8.5) | 5.3 (1.1) | 3.2 (0.9) | 1.3 (0.3) | NR | Aged>70yrs; FPG: 6.1–6.9 mmol/L; A1C: 6.0–6.9% | Recruited from a referral | 15.0 |

(Continued)
| Citation               | Sample size | Length of follow-up (months) | Age at BL (years) | Sex (% female) | Setting: Race/ethnicity | BMI at BL (kg/m²) [mean (SD)] | SBP/DBP at BL (mmHg) [mean (SD)] | TC at BL (mmol/L) [mean (SD)] | LDL/HDL at BL (mmol/L) [mean (SD)] | TG at BL (mmol/L) [mean (SD)] | Inclusion criteria                                                                 | Sampling method                              | Attrition (%) |
|-----------------------|-------------|------------------------------|-------------------|----------------|------------------------|------------------------------|-------------------------------|-------------------------------|---------------------------------|---------------------------------|--------------------------------------------------------------------------------|----------------------------------------------|--------------|
| Kanaya et al. 2012    | 238         | 12                           | 56.5 (16.5)       | 73.5           | Community, Berkeley, CA | 30.0 (5.7)                   | 127.2 (20.0) VR               | NR                            | 3.0 (1.3)                       | 1.6 (1.2)                       | Aged 25-54 yrs, capillary blood glucose <100 mg/dL, without DM                  | Recruited from a community education outreach     | 12.2         |
| Kanaya et al. 2014    | 180         | 12                           | 95.0 (7.0)        | 72.0           | Community, San Francisco, CA | 34.3 (6.7)                   | 124.0 (14.0) VR              | 5.3 (1.0)                      | 3.2 (0.9)                       | 1.8 (0.8)                       | Aged 21-65 yrs, with MetS (FPG 100-125 mg/dL), HT, and unfavorable lifestyle (<1500 kcal of moderate intensity activity), without DM | Recruited by ads and flyers in community and clinical settings                       | 21.1         |
| Khalk et al. 2010     | 301         | 24                           | 57.9 (9.5)        | 57.5           | Community, Winston-Salem, NC | 32.7 (4.8)                   | NR                            | NR                            | NR                             | NR                             | Patients with pre-DM defined by FPG of 95-125 mg/dL and BMI of 25-39 kg/m² and without DM and CVD | Recruited from mass mailing, community health fair or referrals                     | 12.6         |
| Kawano et al. 2009    | 217         | 17                           | 60.9 (13.8)       | 68.5           | Community, Tokyo, Japan | 23.7 (4.4)                   | 127.5 (17.5) VR              | 5.3 (0.9)                      | 3.1 (0.7)                       | 1.5 (0.4)                       | People with FPG: 100-140 mg/dL, or A1C: 5.5-6.0%                                | Recruited from health checkup                     | 27.2         |
| Keogh et al. 2007     | 36          | 12                           | 48.6 (5.2)        | 68.0           | Community, Adelaide, Aus.  | 32.9 (4.5)                   | 122.0 (10.0) VR              | 5.5 (1.4)                      | 3.6 (1.9)                       | 1.3 (0.6)                       | Overweight or obese people, aged 20-65 yrs; BMI: 27-40 kg/m², without DM, with FPG: 70-99 mg/dL | Recruited from newspaper ads                        | 30.6         |
| Lawton et al. 2009    | 1089        | 24                           | 58.9 (8.9)        | 100.0          | Clinic, Wellington, New Zealand | 29.2 (6.0)                   | 123.1 (17.5) VR              | 6.1 (1.2)                      | 2.4 (1.1)                       | 1.3 (0.6)                       | Physically inactive women, aged 40-74 yrs without medical condition              | Recruited by invitation letters or practice register | 7.4          |
| Lim et al. 2010       | 113         | 12                           | 47.0 (10.0)       | 82.3           | Community, Adelaide, Aus.  | 32.0 (6.0)                   | 127.0 (12.3) VR              | 5.6 (1.0)                      | 2.9 (1.7)                       | 1.3 (0.6)                       | Aged 20-65 yrs; BMI: 28-40 kg/m², with or without DM                              | Recruited by ads                               | 38.9         |
| Lombard et al. 2010   | 350         | 12                           | 40.4 (4.8)        | 100.0          | Community, Melbourne, Aus.  | 27.8 (5.4)                   | NR                            | NR                            | 4.9 (0.9)                       | 2.6 (1.4)                       | Women with a child in schools without pregnancy and serious medical conditions | Recruited through an invitation attached to school newsletter                      | 14.0         |
| Ma et al. 2009/2013   | 241         | 15                           | 52.9 (10.6)       | 47.0           | Clinic, San Francisco, CA | 32.0 (5.4)                   | 118.8 (11.7) VR              | 4.9 (0.9)                      | 2.8 (1.9)                       | 1.2 (0.3)                       | Patients aged ≥18 yrs; BMI: 25 kg/m², with pre-DM defined by FPG of 100-125 mg/dL, or MetS | Recruited from a single primary care clinic                      | 8.3          |
| Marzetti et al. 2016  | 225         | 12                           | 52.0 (11.0)       | 84.4           | Community, Indianapolis, IN | 36.8 (7.2)                   | 130.2 (14.0) VR              | 4.9 (0.9)                      | 2.4 (1.2)                       | 1.2 (0.8)                       | Aged 18-55 yrs, BMI: 24 kg/m² (> = 23 kg/m² for Asian); ADA risk score: ≥2; A1C: 5.7-6.5% | Recruited from a screening program                 | 22.2         |
| Marsh et al. 2010     | 96          | 12                           | 30.2 (5.2)        | 100.0          | Clinic, Sydney, Aus.        | 34.5 (4.2)                   | NR                            | NR                            | 4.8 (0.7)                       | 2.8 (0.7)                       | Men, aged: 18-40 yrs; BMI: 25 kg/m², with prandial ovary syndrome, without pregnancy and DM | Recruited from a screening program              | 49.0         |
| Mason et al. 2016     | 194         | 12                           | 47.0 (12.7)       | 78.0           | Community, San Francisco, CA | 35.5 (3.6)                   | NR                            | NR                            | NR                             | NR                             | Obese adults aged ≥18 yrs; BMI: 30-45 kg/m², WC: <102 cm for males, <88 cm for females, without DM, confirmed by FPG 130 mg/dL | Recruited from community by newspaper ads          | 23.2         |
| McAuley et al. 2005/06 | 326        | 12                           | Range: 30-70      | 100.0          | Community, Dunedin, New Zealand | 35.7 (0.0)                   | 126.8 (13.0) VR              | 5.8 (1.0)                      | 3.8 (0.9)                       | 1.2 (0.3)                       | Aged 30-70 yrs; BMI: 27 kg/m², without pregnancy                                | Recruited by local ads                           | 18.3         |
| Mellberg et al. 2014  | 70          | 24                           | 59.9 (5.7)        | 100.0          | Community, Umea, Sweden     | 32.7 (3.5)                   | 126.5 (13.0) VR              | 5.7 (1.1)                      | 3.8 (1.0)                       | 1.4 (0.4)                       | Postmenopausal smoking women, BMI: 27 kg/m², without DM, FPG: 5-7 mmol/L            | Recruited by newspapers ads                     | 30.0         |
| Muto et al. 2001      | 326         | 18                           | 42.5 (3.7)        | 0.0            | Community, Tokyo, Japan     | 24.7 (3.0)                   | 123.2 (15.6) VR              | 5.5 (0.9)                      | 2.2 (1.4)                       | 1.2 (0.4)                       | Male workers with at least one abnormality, including FPG >100 mg/dL               | Recruited from a building maintenance company       | 7.4          |
| Narayan et al. 1998   | 95          | 12                           | Range: 35-50      | 75.8           | Clinic, Pusa, A2            | 30.2 (5.9)                   | Range: 90.0-176              | Range: 2.1-6.1                  | Range: 0.3-3.6                   | Range: 0.6-1.0                   | Overweight/obese people, aged ≥25-64 yrs, BMI: >25 kg/m² without DM, OGTT ≤7 mmol/L | Recruited from an epidemiologic study             | 2.0          |
| Nilsson et al. 1992   | 94          | 12                           | 55.0 (7.2)        | NR             | Community, Dalby, Sweden    | 81.4 (11.6)                  | 145.0 (18.0) VR              | 5.6 (0.8)                      | 3.9 (0.7)                       | 0.9 (0.2)                       | Patients with or without HT, but no DM                                         | Recruited from a cross-sectional study            | 8.5          |
| Citation | Sample site | Length of follow-up (months) | Age at BL (years) | Sex (% female) | Setting: Race/ethnicity | TC at TL (mmol/L) | LDL/HDL at TL (mmol/L) | TG at TL (mmol/L) | Inclusion criteria | Sampling method | Attrition (%) |
|-----------------|-------------|---------------------------|-----------------|---------------|-----------------------|------------------|------------------------|------------------|-----------------|----------------|--------------|
| Nilsson et al. 2001 | 113 | 18 | 40.7 (0.2) | 60.9 | Community Helsingborg Sweden | 27.8 (5.6) | 132.5 (18.0) | 77.4 (9.7) | 5.8 (0.9) | 3.9 (0.9) | 1.2 (0.3) | Older: 40-55yrs; with a cardiovascular risk score sum of >9 | Recruited from a screening program | 18.6 |
| Dider et al. 2012 | 312 | 12 | 52.0 (11.0) | 74.4 | Community Lawrence MA | 33.9 (5.6) | 128.7 (12.4) | NR | NR/ NR | NR | Age: 25-50yrs; BMI >24.9 kg/m², with risk for DM, but without DM | Recruited from the Greater Lawrence Family Health Center | 7.4 |
| Poston et al. 2005 | 250 | 12 | 41.0 (8.1) | 60.9 | Community Austin TX | 30.1 (3.1) | 121.5 (17.3) | 123.3 (8.6) | 5.2 (1.0) | 3.1 (1.4) | 0.8 (0.4) | Overweight/obese people, aged: 25-50yrs; BMI: 27-40 kg/m² without DM or pregnancy, FPG >7 mmol/L, confirmed by OGTT | Recruited from a screening program | 45.6 |
| Potteger et al. 2003 & 2002 | 66 | 16 | NR | 57.6 | Community Denver CO | Range: 25-34.9 | NR/ NR | NR/ NR | NR | Sedentary people without DM and heart disease | Recruited from the MidWest Exercise Trial | 10.1 |
| Reid et al. 2014 | 406 | 12 | 51.1 (11.6) | 61.3 | Clinic Ottawa Canada | 29.4 (5.7) | 121.1 (16.1) | 76.5 (9.5) | 5.2 (1.0) | 3.3 (0.9) | 1.3 (0.4) | Obese people with coronary risk, without DM, with DM, FPG <7 mmol/L | Recruited from a care centre for healthy adults | 25.8 |
| Rosser et al. 1997 | 93 | 12 | 41.0 (NR) | 67.7 | Clinic Stockholm Sweden | 38.7 (4.5) | 136.3 (16.3) | 86.5 (12.3) | 5.7 (0.9) | NR/ NR | 1.9 (1.0) | Older: 30-55yrs; with DM | Recruited from hospital waiting list | 38.7 |
| Ryttig et al. 1997 | 81 | 28 | 42.5 (10.0) | 54.3 | Clinic Stockholm Sweden | 37.7 (4.6) | 136.2 (17.6) | 85.3 (9.9) | 5.7 (1.0) | NR/ 1.1 (0.2) | 2.0 (1.2) | Obese people, aged: 21-64yrs; BMI >30 kg/m², without DM and pregnancy | Recruited from hospital waiting list | 4.9 |
| Sartorelli et al. 2005 | 104 | 12 | 46.5 (9.1) | 79.8 | Clinic Sao Paulo Brazil | 29.7 (2.5) | 116.6 (17.6) | 77.5 (18.3) | 5.3 (1.3) | 3.6 (1.7) | 1.2 (0.4) | Overweight or obese people, aged: 30-65yrs; BMI: 34-35 kg/m² without DM, or pregnancy | Recruited from a screening of high-risk group for DM | 31.7 |
| Safin et al. 2016 | 604 | 12 | 46.5 (10.9) | 83.0 | Clinic Aarhus GA | 35.7 (7.3) | 130.5 (16.6) | 82.6 (8.7) | NR/ NR | NR | African Americans aged: 20-64yrs; BMI >30 kg/m², without DM, confirmed by FPG <7 mmol/L | Recruited from church | 0.0 |
| Simkin-Silverman et al. 1995 & 1998 & 2003 & 2006 & 2012 | 535 | 54 | 47.0 (11.0) | 100.0 | Community Allonby PN | NR | 110.0 (12.8) | 64.0 (9.2) | 4.9 (0.6) | 3.0 (0.6) | 1.5 (0.3) | Premenopausal women, aged: 44-65yrs; BMI: 20-34 kg/m², FPG <7.8mmol/L | Recruited from the Women’s Healthy Lifestyle Project | 2.8 |
| Siu et al. 2015 | 182 | 12 | 56.0 (9.1) | 74.2 | Community Hong Kong China | NR | 133.8 (16.8) | 82.4 (9.8) | NR/ NR | NR | Older: 55-65yrs; with MeB >1 BC; BMI 30 cm for males; (2) BMI >30 cm for females | Recruited from a screening | 35.7 |
| Stalen et al. 2004 | 361 | 12 | 57.2 (4.8) | 100.0 | Community Tucson AZ 100% Hispanic | 29.5 (5.3) | 124.8 (16.7) | 74.1 (9.6) | 5.6 (1.3) | NR/ NR | NR | Uninsured Hispanic women, aged: 50yrs | Recruited from clinic registration | 33.4 |
| Stelmack et al. 1998 | 377 | 12 | 52.1 (7.3) | 47.7 | Community Palo Alto CA | 26.7 (3.0) | 115.5 (12.8) | 73.2 (7.4) | 6.2 (0.6) | 4.2 (0.5) | 1.2 (0.2) | Postmenopausal women, aged: 45-64yrs; men aged: 30-64yrs, BMI <30 kg/m², without DM, FPG <7 mmol/L, OGTT confirmed | Recruited from the Diet and Exercise for Healthy lifestyle Program | 27.0 |
| Tapsell et al. 2014 | 120 | 12 | 48.9 (9.3) | 75.0 | Community Wollongong Australia | 30.0 (2.7) | NR/ NR | NR | 5.2 (0.9) | 3.2 (0.8) | 0.8 (0.2) | Healthy adults aged 18-65yrs, BMI: 25-34 kg/m², without DM | Recruited by ads in the local media | 22.5 |
| ter Bogt et al. 2009 | 407 | 12 | 56.1 (7.8) | 57.9 | Community Ballina The Netherlands | 29.6 (3.4) | 145.5 (17.0) | 86.5 (9.9) | 5.6 (1.0) | 3.5 (0.9) | 1.4 (0.4) | Overweight or obese people, aged: 40-70yrs; BMI: 25-40 kg/m² with HT or dyslipidemia, without DM | Recruited from a screening program | 9.0 |
| Thompson et al. 2005 | 90 | 12 | 41.4 (8.9) | 85.6 | Clinic Kruisla TK | 34.8 (3.1) | NR/ NR | NR | 5.0 (0.9) | 3.1 (0.9) | 1.0 (0.4) | Obese people, aged: 25-70yrs; BMI: 30-40 kg/m² without DM or pregnancy | Recruited from an ad program | 13.3 |
| Tsai et al. 2010 | 50 | 12 | 49.4 (11.9) | 88.0 | Clinic Philadelphia PA | 36.5 (0.8) | 129.4 (12.2) | 80.7 (8.2) | 4.9 (0.9) | 3.0 (0.9) | 1.0 (0.3) | Overweight or obese people with BMI: 25-40 kg/m², without serious psychiatric illness | Recruited from flyers, and referrals from PCPs | 6.0 |
| Vainio et al. 2007 | 120 | 12 | Range: 35-40 | 100.0 | Community Oulu Finland | 25.3 (4.6) | NR/ NR | NR | 5.3 (0.9) | 3.2 (0.8) | 1.7 (0.4) | Women aged: 35-40yrs, without chronic disease | Recruited from the National Population Register of Finland | 33.3 |
| Vetter et al. 2013 | 390 | 24 | 51.5 (11.5) | 79.7 | Clinic Philadelphia PA | 38.5 (4.7) | 121.4 (16.3) | 76.2 (10.4) | 4.6 (1.0) | 2.9 (0.9) | 1.1 (0.3) | Older: 21-74yrs; BMI: 25-40 kg/m²; with M+T (FPG ≥110 mmol/L), without cardiovascular events | Recruited from primary care practices | 13.8 |

(Continued)
Table 1. (Continued)

| Citation                  | Sample size | Length of follow-up (years) | Sex (% female) | Setting: Race/ethnicity | BM at BL (kg/m²) [mean (SD)] | SBP/DBP at BL (mmHg) [mean (SD)] | TC at BL (mmol/L) [mean (SD)] | LDL/HDL at BL (mmol/L) [mean (SD)] | TG at BL (mmol/L) [mean (SD)] | Inclusion criteria                                      | Sampling method                          | Attrition (%) |
|--------------------------|-------------|-----------------------------|----------------|------------------------|------------------------------|----------------------------------|-------------------------------|-----------------------------------|-------------------------------|----------------------------------------------------------|-------------------------------------------|---------------|
| von Thiele Schwarz et al. 2008 | 195         | 12                          | 100.0          | Community Stockholm Sweden | NR                           | 114.0 (16.9)                   | 5.2 (1.0)                    | 2.9 (0.8)/1.8 (0.4)                 | 1.0 (0.6)                     | Working age women without DM and pregnancy               | Recruited from a public dental health care organization | 9.2            |
| Watanabe et al. 2003     | 173         | 12                          | 91.1 (7.1)     | Community Tokyo Japan   | 24.4 (2.9)                   | 121.7 (14.4)                   | 5.2 (0.9)                    | NR/1.4 (0.4)                      | 1.4 (0.8)                     | Male workers with risk for DM, aged:35-70yrs; OGTT confirmed | Recruited from annual check-up list           | 9.8            |
| Werniski et al. 1998     | 45          | 23                          | 100.0          | Community Syracuse NY   | 35.9 (0.0)                   | NR/NR                          | NR/NR                        | NR/NR                            | NR/NR                         | Women without DM, CAD, and pregnancy                    | Recruited from a cohort study                | 0.0            |
| Weiss et al. 2006        | 48          | 12                          | 56.8 (3.0)     | Community St. Louis MO  | 27.3 (2.1)                   | NR/NR                          | NR/NR                        | NR/NR                            | NR/NR                         | Sedentary people, aged:50-60yrs; BMI:23.5-29.9kg/m²; non-smoker without DM, FPG<7mmol/L, OGTT confirmed | Recruited from newspaper or radio ads            | 21.3           |
| Wing et al. 1995         | 302         | 18                          | 37.4 (3.3)     | Community Pittsburgh PA | 30.9 (2.1)                   | 111.7 (10.7)                   | 5.0 (0.8)                    | NR/1.2 (0.2)                      | 1.2 (0.7)                     | Aged:25-45yrs; 13.6–31.8 kg above ideal body weight, without serious disease | Recruited from newspaper or radio ads            | 22.0           |
| Wing et al. 1998         | 154         | 24                          | 45.7 (4.4)     | Community Pittsburgh PA | 35.9 (4.3)                   | 116.7 (14.9)                   | 5.0 (0.8)                    | 3.1 (0.8)/1.2 (0.3)               | NR/NR                         | Overweight people, aged:40-59yrs; with diabetic parents | Recruited from newspaper or radio ads            | 22.0           |
| Wychoveley et al. 2012   | 123         | 12                          | 90.8 (9.3)     | Clinic Adelaide Australia | 33.0 (0.3)                   | 155.1 (12.5)                   | 5.2 (0.9)                    | 3.2 (0.8)/1.3 (0.4)               | 1.7 (0.7)                     | Overweight or obese males, aged:20-65yrs; BMI:20-27 kg/m², without DM | Recruited by a screening program               | 44.7           |
| Yeh et al. 2016          | 60          | 12                          | 58.9 (10.9)    | Community New York 100% Asian | 28.1 (2.4)                   | 125.9 (16.1)                   | 4.8 (1.0)                    | 2.8 (0.9)/1.4 (0.3)               | 1.4 (0.7)                     | Patients with pre-DM defined by A1C:5.7–6.4% and BMI <6kg/m² | Recruited from hospital record                 | 3.3            |
| Mean (SD)                | 50.6 (8.7)  | 30.5 (4.6)                  | 127.5 (15.3)   | 79.2 (9.3)              | 5.4 (1.0)                    | 3.3 (0.9)/1.3 (0.3)            | 1.5 (0.9)                    |                                                                  |                                             |                                                          |                                             | 0-62.0        |

**Total Range**: 12-64 [95.6-127.5]

Abbreviations: BG: blood glucose; BL: baseline; BMI: body mass index; CAD: coronary Artery Disease; CVD: cardiovascular disease; DBP: diastolic blood pressure; DM: diabetes mellitus; FBG: fasting blood glucose; FPG: fasting plasma glucose; HDL-C: high density cholesterol; HT: hypertension; IGT: impaired glucose tolerance; LDL-C: low density cholesterol; MetS: metabolic syndrome; min/w: minutes/week; NR: not reported; OGTT: oral glucose tolerance test; PG: plasma glucose; SD: standard deviation; TC: total cholesterol; TG: triglycerides.

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recruited through screening programs. Attrition ranged from 0% to 60%, and in 16 studies, [21,34–36,45,60,62,66,69,74,76,78,81,82,86,94] attrition was 30% or more; longer follow-up resulted in higher attrition. Thirty-nine studies with mean FPG < 5.5 mmol/L or mean A1C < 5.5% were classified as low range group, and 40 studies with mean FPG ≥ 5.5 mmol/L or mean A1C ≥ 5.5% were classified as high range group.

We observed considerable heterogeneity in the treatments provided to both intervention and comparison groups (Tables A&B in S1 File). In 29 studies, a similar approach was used in both intervention and control groups: data from these studies were synthesized by a single arm model, and are presented in Table C in S1 File as an online supplement. In the other 50 studies, UC was used in the control group. In the 50 studies that compared an intervention to UC, 38 had two arms, 5 studies [49,64,87,88,91] had 3 arms, and 7 studies [13,24,28,44,54,62,93] had 4 arms (e.g., PA, D, PA+D and control arm). The randomization procedure was described in 48 studies (Table B in S1 File). In 29 studies, allocation concealment was adequately reported. Meta-regression analyses indicated that there was no significant interaction between the between-group change in FPG and all study-level characteristics, such as mean age, publication date, the length of F/U, number of contacts, attrition, and their interaction terms. An Egger’s plot demonstrated a symmetrical shape distribution (except for two outliers) which is consistent with no publication bias.

Changes in CVD risk factors

In 57 studies or study arms comparing interventions to UC with attrition < 30%, the pooled effect estimate from all studies demonstrated that compared to UC, all lifestyle interventions,
including PA, D, or PA+D interventions, achieved significant improvements in SBP (-2.05mmHg [95%CI -2.81, -1.28]), DBP (-1.65mmHg [-2.16, -1.14]), TC (-0.09mmol/L [-0.14, -0.04]), LDL-C (-0.08mmol/L [-0.13, -0.03]), HDL-C (0.03mmol/L [0.01, 0.04]), and TG (-0.08mmol/L [-0.14, -0.03]) (Table 2). When including the 15 studies with attrition ≥30% in the sensitivity analysis, we observed similar effects. The remaining results are limited to studies with attrition <30%.

**Comparison according to participant baseline glycemic level**

In the 39 studies among persons with low range glycemic level, lifestyle interventions were associated with significantly improved SBP (-0.95mmHg [-1.75, -0.15]), DBP (-1.40mmHg [-2.24, -0.56]), LDL-C (-0.08mmol/L [-0.14, -0.02]), and HDL-C (0.01mmol/L [0.00, 0.03]), except for TC (-0.06mmol/L [-0.13, 0.01]) and TG (-0.04mmol/L [-0.10, 0.02]). In the 40 studies among persons with high range glycemic level, lifestyle interventions significantly improved most CVD risk indicators, and the improvements were more substantial: SBP (-2.89mmHg [-3.95, -1.83]), DBP (-1.83mmHg [-2.50, -1.17]), TC (-0.12mmol/L [-0.18, -0.05]), LDL-C (-0.10mmol/L [-0.18, -0.01]), HDL-C (0.04mmol/L [0.02, 0.06]), and TG (-0.12mmol/L [-0.21, -0.04]).

**Comparison according to intervention modality**

Analyses stratified by intervention types showed that PA+D vs UC achieved the best incremental improvements in SBP (-2.29mmHg [-3.19, -1.40]), DBP (-1.66mmHg [-2.24, -1.09]), TC (-0.10mmol/L [-0.16, -0.05]), LDL-C (-0.08mmol/L [-0.14, -0.02]), HDL-C (0.03mmol/L [0.02, 0.05]), and TG (-0.07mmol/L [-0.13, -0.01]). D vs UC showed significant improvements in two categories: DBP (-2.28mmHg [-4.07, -0.49]), TC (-0.17mmol/L [-0.34, -0.01]); improvements in other measures did not reach statistical significance. Improvements with PA vs UC did not reach statistical significance in any category: SBP (-0.72mmHg [-1.89, 0.44]), DBP (-1.12mmHg [-2.34, 0.10]), TC (-0.02mmol/L [-0.09, 0.06]), LDL-C (-0.03mmol/L [-0.18, 0.12]), HDL-C (0.01mmol/L [-0.02, 0.04]), and TG (-0.10mmol/L [-0.22, 0.02]). Pooled effects of CVD risk reduction are presented in Figs 2–7.

**Comparison according to length of follow-up**

In 34 studies or study arms with 12 months of follow-up, lifestyle interventions significantly improved all CVD risk factors: SBP (-2.07mmHg [-3.19, -0.95]), DBP (-1.62mmHg [-2.29, -0.95]), TC (-0.06mmol/L [-0.10, -0.01]), LDL-C (-0.08mmol/L [-0.13, -0.02]), HDL-C (0.02mmol/L [0.01, 0.03]), and TG (-0.08mmol/L [-0.14, -0.03]). For 7 studies or study arms with 13–23 months of follow-up, significant improvements were observed in four CVD risk factors: SBP (-1.73mmHg [-2.80, -0.65]), DBP (-1.25mmHg [-2.02, -0.48]), TC (-0.19mmol/L [-0.26, -0.11]), and LDL-C (-0.12mmol/L [-0.19, -0.05]). When the follow-up was ≥24 months (n = 14), significant improvements remained visible only for: SBP (-1.58mmHg [-2.71, -0.45]), DBP (-1.36mmHg [-2.30, -0.41]), and HDL-C (0.05mmol/L [0.02, 0.08]).

**Correlation between interventional effects on CVD risk reduction and glucose change and weight loss effect sizes**

Findings from meta-regression analyses demonstrated that except for LDL-C category, Pearson’s correlation, r between CVD risk reduction effect sizes and glucose effect sizes ranged from 0.73 to 0.83 in SBP, DBP, TC, HDL-C, and TG, but r between CVD risk reduction effect sizes and baseline FPG were very low, only ranging from 0.26 to 0.44 in SBP, DBP, TC,
### Table 2. Lifestyle interventional effect: Meta-analyses results.

|                | SBP (mmHg) | DBP (mmHg) | TC (mmol/L) | LDL-C (mmol/L) | HDL-C (mmol/L) | TG (mmol/L) |
|----------------|------------|------------|-------------|----------------|----------------|-------------|
|                | Studies (sample size) | Pooled mean (effect size) (95% CI) | Heterogeneity p value | Studies (sample size) | Pooled mean (effect size) (95% CI) | Heterogeneity p value | Studies (sample size) | Pooled mean (effect size) (95% CI) | Heterogeneity p value | Studies (sample size) | Pooled mean (effect size) (95% CI) | Heterogeneity p value |
| LI vs UC (all studies *) | 42 (8331) | -2.05 (0.06) (-2.81, -1.28) | <0.01 | 39 (7631) | -1.65 (0.07) (-2.16, -1.14) | <0.01 | 36 (6925) | -0.09 (0.04) (-0.14, -0.04) | <0.01 | 27 (4563) | -0.08 (0.05) (-0.13, -0.03) | <0.01 |
| LI vs UC (all studies 1) | 50 (9053) | -2.13 (0.04) (-2.88, -1.38) | <0.01 | 46 (8261) | -1.57 (0.06) (-2.07, -1.07) | <0.01 | 44 (7541) | -0.11 (0.05) (-0.16, -0.06) | <0.01 | 34 (5087) | -0.09 (0.04) (-0.15, -0.04) | <0.01 |
| LI vs UC (Group 1) | 17 (3492) | -0.95 (0.04) (-1.75, -0.15) | 0.02 | 15 (2949) | -1.40 (0.06) (-2.24, -0.56) | <0.01 | 16 (2904) | -0.06 (0.03) (-0.13, -0.01) | <0.01 | 15 (3065) | -0.08 (0.05) (-0.14, -0.02) | 0.01 |
| LI vs UC (Group 2) | 25 (4839) | -2.89 (0.08) (-3.95, -1.83) | <0.01 | 24 (4682) | -1.83 (0.08) (-2.50, -1.17) | <0.01 | 20 (4021) | -0.12 (0.06) (-0.18, -0.05) | <0.01 | 12 (1498) | -0.10 (0.06) (-0.18, -0.01) | 0.02 |
| LI vs UC (F/ U = 12m) | 34 (6616) | -2.07 (0.05) (-3.19, -0.95) | <0.01 | 31 (5916) | -1.62 (0.06) (-2.29, -0.95) | <0.01 | 29 (5813) | -0.06 (0.04) (-0.11, -0.01) | <0.01 | 23 (3643) | -0.08 (0.05) (-0.13, -0.02) | <0.01 |
| LI vs UC (F/ U = 13-23m) | 6 (1418) | -1.73 (0.08) (-2.80, -0.65) | 0.98 | 6 (1436) | -1.25 (0.08) (-2.02, -0.48) | 0.60 | 6 (974) | -0.19 (0.17) (-0.26, -0.02) | 0.46 | 5 (1033) | -0.12 (0.10) (-0.19, -0.05) | 0.36 |
| LI vs UC (F/ U >24m) | 14 (3123) | -1.58 (0.05) (-2.71, -0.45) | <0.01 | 14 (3122) | -1.36 (0.05) (-2.30, -0.41) | <0.01 | 13 (2788) | -0.07 (0.03) (-0.17, -0.02) | <0.01 | 5 (543) | 0.06 (0.04) (-0.07, 0.20) | 0.39 |
| PA vs UC | 7 (1466) | -0.72 (0.03) (-1.89, -0.44) | 0.22 | 7 (1465) | -1.12 (0.05) (-2.34, -0.10) | 0.22 | 6 (1429) | -0.02 (0.01) (-0.09, 0.00) | 0.76 | 3 (256) | -0.03 (0.02) (-0.18, 0.12) | 0.91 |
| D vs UC | 4 (263) | -1.45 (0.07) (-3.83, 0.94) | 0.23 | 4 (263) | -2.28 (0.16) (-4.07, -0.49) | 0.74 | 3 (228) | -0.17 (0.13) (-0.34, -0.01) | 0.89 | 3 (228) | -0.14 (0.11) (-0.30, 0.02) | 0.99 |
| PA+D vs UC | 31 (6602) | -2.29 (0.06) (-3.19, -1.40) | <0.01 | 28 (5903) | -1.66 (0.07) (-2.24, -1.09) | <0.01 | 27 (5268) | -0.10 (0.05) (-0.16, -0.05) | <0.01 | 21 (4079) | -0.08 (0.04) (-0.14, -0.02) | <0.01 |

Abbreviations: D: dietary; DBP: diastolic blood pressure; HDL-C: high density lipoprotein cholesterol; LDL-C: low density lipoprotein cholesterol; LI: lifestyle intervention; m: month; NA: not applicable; PA: physical activity; SBP: systolic blood pressure; TC: total cholesterol; TG: triglycerides; UC: usual care; vs: versus

* All studies with attrition <30%.
† All studies with attrition <30% plus studies with attrition ≥30%.
‡ All studies with attrition <30% and participants with FPG<5.5 mmol/L or A1C<5.5%.
§ All studies with attrition <30% and participants with FPG≥5.5 mmol/L or A1C≥5.5%.
HDL-C, and TG. The r between CVD risk reduction effect sizes and weight followed the same patterns: except for LDL-C category, r between CVD risk reduction effect sizes and weight loss effect sizes ranged from 0.51 to 0.75 in SBP, DBP, TC, HDL-C, and TG, but r between CVD risk reduction effect sizes and baseline weight were very low, only ranging from 0.02 to 0.30 in SBP, DBP, TC, HDL-C, and TG. Compared to weight loss, glucose response is a better indicator of the CVD risk factor response because the glucose response has a stronger correlation with the CVD risk factor response as r ranges showed above (Table 3).

**Discussion**

In this review of the effectiveness of lifestyle interventions on the reduction of CVD risk factors among adults with low glycemic levels (below the IGT threshold), we found that lifestyle interventions, including physical activity, diet, and behavioral modification, can significantly improve CVD risk profiles, including SBP, DBP, TC, HDL-C, and TG. When stratified by glycemic levels, we found similar intervention effects between studies of participants with low vs high-range glycemic levels, except for TC and TG. Greater improvements were observed among studies with 12 months of follow-up than those with longer follow up, such that only SBP, DBP, and HDL-C improvements were sustained after 24 months. Studies that used a combined strategy of PA and D had the strongest effect on improving CVD profiles, followed by studies using D interventions only; studies only using a PA intervention strategy had the weakest effect. We have previously reported that multi-faceted interventions combining PA and D are effective in improving glucose regulation in populations with average low-range and high-range glucose levels. The results of the present analyses suggest the effect of such interventions also applies to traditional biologic CVD risk factors.
Lifestyle interventional effects on CVD risk reduction observed in our studies among people without IGT or diabetes are consistent with those from the main trials of diabetes prevention among persons with IGT. For example, the US Diabetes Prevention Program (DPP) Study among people with IGT reported improvements in CVD profiles for all categories as measured by the mean differences between lifestyle intervention and placebo groups. The magnitude of improvements in CVD profiles in the DPP[126] in 1-year follow-up are consistent with those from our review (DPP vs this review: SBP, -2.50 vs -2.07 mmHg; DBP, -2.71 vs -1.62 mmol/L; TC, -0.06 vs -0.06 mmol/L; LDL-C, -0.02 vs -0.08 mmol/L; HDL-C, 0.01 vs 0.02 mmol/L; TG, -0.18 vs. -0.08 mmol/L, respectively). This comparison is also true for other major diabetes prevention trials (e.g., Finish Diabetes Prevention Study).[127]

Our findings may have important implications for decision makers in the areas of both diabetes and CVD primary prevention. Our meta-regression analyses indicated that the magnitude of improvements in CVD risk profiles is less correlated with baseline glucose level, but highly correlated with the effect sizes of glucose improvement. Meanwhile, the meta-regression analyses also indicated that the magnitude of improvements in CVD risk profiles is less correlated with baseline body weight, but highly correlated with the effect sizes of weight loss. We thus conclude that lifestyle interventions may provide important benefits across the full distribution of glycemic levels and body weight, including populations with glycemic levels below the IGT threshold, for both the low and high ranges of baseline FPG, and for populations with normal weight but with CVD risk factors. However, economic factors as well as the effectiveness of interventions influence decisions regarding the types of interventions provided to individuals with glycemic levels below the IGT threshold.[128,129] The cost-effectiveness of

Fig 3. changes in diastolic blood pressure in the intervention versus usual care groups (mmHg).

Group 1: low-range glycemic group (FPG<5.5mmol/L or A1C<5.5%). Group 2: high-range glycemic group (FPG ≥5.5mmol/L or A1C ≥5.5%). D, diet, PA, physical activity, UC, usual care, vs, versus.

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lifestyle interventions that can simultaneously reduce diabetes and CVD risk among individuals with glycemic levels below the IGT threshold should be examined.

Our findings demonstrate that lifestyle interventions, compared to UC, achieved improvement in both diabetes prevention and CVD risk reduction, and these improvements were not only statistically significant, but also have clinical relevance. Previous studies indicated that each 0.03 mmol/L increase in HDL-C is associated with the reduction of coronary heart disease risk by 2–3%,[130] and each 5 mmHg reduction in SBP and 2 mmHg reduction in DBP reduce stroke risk by 13% and 11.5%, respectively.[131] According to an epidemiology study, a 1% decrease in total cholesterol leads to a decrease in the incidence of coronary events by 2%. [132] One study also indicated that weight loss improved CVD profiles because each kilogram change in body weight was related to the change in the risk of coronary heart disease by 3.1%. [133]

Given that lifestyle intervention program participants in our reviewed studies usually achieved improvements in CVD across a full spectrum of outcomes simultaneously, the overall combined benefits brought by lifestyle interventions could be amplified. An estimation of overall effect on CVD risk would be helpful for our understanding the importance of interventional impact. Unfortunately, although there are several models available for CVD risk calculation (e.g., Framingham Risk Score,[134] and the ACC/AHA CVD risk calculator[135]), we are not aware of any available estimation model by which we can calculate the overall combined effect of changes of different individual risk factor. Further research and validation test, therefore, maybe needed for creating this model. If this kind model is available in the future, we can apply this model to our meta-analytic findings to estimate the overall combined effect of...
changes of different individual risk factor. For example, if a population, through lifestyle and behavior changes, achieved CVD risk reductions as much as showed in our meta-analyses, we can estimate the overall health benefits (e.g., how many CVD events can be prevented in the future). Despite this unavailability, the improvement in glucose regulation[125] coupled with our findings regarding the improvement in CVD risk reduction suggested that lifestyle interventions can achieve a comprehensive improvement goal as stated in AHA Special Report[17] of preventing CVD and diabetes simultaneously among persons with lower diabetes risk.

Strong evidence shows that PA programs have important independent effects on non-insulin-mediated glucose transport, markers of inflammation, insulin resistance, blood pressure, lipid profile, fitness, and improved lean-to-fat mass ratio.[136] Our findings suggest that these effects were more likely observed in studies using multi-component interventions, including PA, calorie restriction, and behavioral support but less so for PA-only interventions. This finding may be related to methodological shortcomings in exercise-only interventions such as low adherence, insufficient exercise volume or length of intervention. Previous studies suggest that it may take up to 2 years for a previously sedentary obese individual to attain enough volume of exercise to effectively reduce CVD risk factors, and individuals in unverified, out-patient interventions are less likely to engage in the prescribed amount of exercise.[137,138] However, we previously reported that exercise-only interventions in our included studies significantly reduced FPG and body weight[125] which in turn further prevented diabetes. Since PA-related improvements in glucose regulation and weight loss can lead to reductions in CVD risk profiles, potential indirect benefits should be taken into account when interpreting our findings.

Fig 5. changes in low density lipoprotein cholesterol in the intervention versus usual care groups (mmol/L). Group 1: low-range glycemic group (FPG<5.5mmol/L or A1C<5.5%). Group 2: high-range glycemic group (FPG≥5.5mmol/L or A1C≥5.5%). D, diet, PA, physical activity, UC, usual care, vs, versus.

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Unhealthy lifestyle factors are related to the atherosclerotic process and these long-term exposures lead to the clinical manifestations of cardiovascular events. A previous study also indicated that lifestyle changes, only in the long-term, are likely to lead to CVD risk factor reduction. Our findings demonstrate that the effects of lifestyle changes on the reduction in CVD risk factors reached their highest point at 12 months of follow-up, then gradually decreased over time. This may reflect the fact that the longer-term intervention may be more effective on reducing CVD risks only if participants remain highly adherent to the intended interventions, which is seldom observed. It could be also true that using CVD mortality, rather than CVD risk reduction alone, to measure the long-term effect of lifestyle changes on CVD is more appropriate as the extended legacy findings of the Chinese Da Qing Study indicated.

Because we used a comprehensive search strategy including all major medical databases, we found a large number of eligible studies. Pooled effects based on a large sample size provide more robust findings than those from any single study. Our review has some limitations as well. First, lifestyle interventions were used in heterogeneous settings, among different populations of varying ages, health status, and race/ethnicity background. While the main components of the lifestyle interventions were generally PA and D, each of the strategies had its own requirements in type, dose, intensity, and frequency. UC also had varying definitions among different comparison groups. Heterogeneity across studies was also reflected in the length of intervention, duration and follow-up, and number of sessions. However, our meta-regression analyses found no interactions between the between-group change in glycemic indicators and study-level characteristics. We also stratified our data syntheses by glycemic level, length of...
follow-up, and type of interventions, taking the heterogeneity among included studies into account. Second, although we stratified by level of glycemic risk at the study level, there was considerable heterogeneity within studies, and the nature of aggregated data prevented individual level classification by glucose level. As a result, there was likely considerable overlap in participant characteristics between low range and high range glycemic groups in our study, which may introduce some misclassification bias. Misclassification bias could be also

![Fig 7. Changes in triglycerides in the intervention versus usual care groups (mmol/L). Group 1: low-range glycemic group (FPG<5.5mmol/L or A1C<5.5%). Group 2: high-range glycemic group (FPG≥5.5mmol/L or A1C≥5.5%). D, diet; PA, physical activity; UC, usual care; vs, versus.](https://doi.org/10.1371/journal.pone.0176436.g007)

Table 3. Correlation between CVD Risk Reduction and FPG and Weight.

| CVD risk reduction | Baseline FPG | FPG effect size | Baseline weight | Weight loss effect size |
|-------------------|--------------|-----------------|-----------------|------------------------|
| SBP               | 0.32         | 0.752           | 0.068           | 0.506                  |
| DBP               | 0.259        | 0.728           | 0.023           | 0.58                   |
| TC                | 0.301        | 0.827           | 0.127           | 0.75                   |
| LDL-C             | 0.186        | 0.117           | 0.196           | 0.18                   |
| HDL-C             | 0.437        | 0.82            | 0.301           | 0.708                  |
| TG                | 0.38         | 0.82            | 0.172           | 0.707                  |

Abbreviations: CVD: cardiovascular disease; DBP: diastolic blood pressure; FPG: fasting plasma glucose; HDL-C: high density cholesterol; LDL-C: low density cholesterol; SBP: systolic blood pressure; TC: total cholesterol; TG: triglycerides

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introduced by usage of both FPG and A1C in our review to identify population with low glycemic risks. Although a previous study indicated that the agreement between FPG and A1C is high,[141] they are not equal with each other.[142] Because of this misclassification bias, some individuals identified as with low glycemic risks could actually have glucose metabolism abnormalities. Audiences need to be cautious when interpreting our findings.

Conclusions

Our review is the first comprehensive examination of the impact of lifestyle interventions on risk for progression of dysglycemia and CVD risk reduction among persons below the IGT threshold. This systematic review suggests that lifestyle change is critical to both CVD risk reduction and diabetes prevention across the full spectrum of risk, complementing the major trials of diabetes prevention that focused on persons with IGT. This review also provides supportive evidences for designing strategies aimed at reducing CVD burden as delineated in the AHA Strategic Impact Goal through 2020 and Beyond.[17] Our findings demonstrated that among adults without IGT or diabetes, PA and D interventions, especially combined can significantly improve SBP, DBP, TC, LHL-C, HDL-C, and TG, in addition to glucose regulation and weight loss, and that these risk reductions may further prevent CVD events.

Supporting information

S1 File. Appendix A. Protocol-Study Protocol with Search Strategy.
Appendix B. PRISMA Checklist- Preferred Reporting Items for Systematic Reviews and Meta-Analyses checklist.
Table A. Intervention Characteristics.
Table B. Quality Assessment.
Table C. Lifestyle Interventional Effect: Meta-analyses Results in A Single Arm Model.
Table D. Intervention effect on FPG and percent weight: meta-analyses results.

(DoC)

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Author Contributions

Conceptualization: XZ.
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Formal analysis: XZ.
Investigation: XZ.
Methodology: XZ.
Project administration: XZ.
Software: XZ.
Supervision: XZ.
Validation: XZ.
Visualization: XZ.

Writing – original draft: XZ.

Writing – review & editing: XZ HMD BS GI WT FL MKA KN SG BB PC IGQ UM CDJ JMD JS LSG EWG.

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