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Title: The efficacy of genotype-based dietary or physical activity advice on behaviour change to reduce the risk of CVD, T2DM or obesity: a systematic review and meta-analysis.

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Abstract

Context: Despite clear evidence that adherence to dietary and physical activity advice can reduce the risk of cardiometabolic disease, a significant proportion of the population do not meet recommendations. Personalised advice based on genetic variation has been proposed to motivate behaviour change, although research to date has been contradictory.

Objective: To evaluate the efficacy of genotype-based dietary or physical activity advice on behaviour change in the general population and individuals that are at-risk of CVD or T2DM.

Data sources: MEDLINE, Embase, PsycINFO and the Cochrane Central Register of Controlled Trials (CENTRAL) up to 7th January 2022. Randomised controlled trials of a genotype-based dietary and/or physical activity advice intervention that aimed to change dietary and/or physical activity behaviour were included.

Data extraction: Abstracts of 7899 records were screened, 14 reports from 11 studies met the inclusion criteria.

Data analysis: There was no effect of genotype-based dietary or physical activity advice on dietary behaviour for all studies SMD 0.00 (-0.11 – 0.11, p = 0.98) or when analysed by sub-group; 'at risk' SMD 0.00 (-0.16 - 0.16, p = 0.99); general population SMD 0.01 (-0.14 – 0.16, p = 0.87). Similar findings were identified for physical activity behaviour for all studies SMD -0.01 (-0.10 – 0.08, p = 0.88) or when analysed by sub-group; 'at risk' SMD 0.07 (-0.18 - 0.31, p = 0.59); general population SMD -0.02 (-0.13 – 0.10, p = 0.77). The quality of evidence for the dietary behaviour outcome was low and for the physical activity behaviour outcome it was moderate.

Conclusions: Genotype-based advice does not affect dietary or physical activity behaviour more than general advice or advice based on lifestyle or phenotypic measures. This was consistent in studies that recruited participants from the general population as well as studies that had recruited participants from populations at-risk of CVD or T2DM.

Key words: gene-based advice, dietary behaviour, physical activity behaviour, behaviour change, personalized nutrition.

Introduction

Non-communicable diseases (NCDs) are the leading cause of mortality worldwide and are responsible for 75% of 'premature deaths', defined as deaths of individuals aged between 30 and 69 years. [1,2] The prevention of NCDs has been identified as a key focus in the promotion of health globally, [3] the importance of which has been further highlighted since NCDs are a major risk factor for adverse outcomes in individuals with COVID-19. [4,5] Obesity, type II diabetes mellitus (T2DM) and cardiovascular disease (CVD) are inextricably linked; obesity increases the risk of developing T2DM and both obesity and T2DM increase the risk of CVD. [6,7] Maintaining a healthy diet and being physically active have been identified as key modifiable risk factors for the prevention of obesity, T2DM and CVD. [8–11] Findings from the Global Nutrition Report 2021 suggest that most countries are not on course to meet Global NCD diet-related targets by 2025; specifically, no countries are on course to meet the target of halting the rise in adult obesity. [12]

One factor that has been suggested to explain the lack of response to public health campaigns to encourage healthy behaviours is 'optimistic bias'; the phenomenon by which an individual underestimates their own risk of developing a disease, such as CVD, compared to others. [13] Personal salience of health advice is more difficult to achieve with a 'one size fits all' approach and has been identified as a key issue in the successful delivery of behaviour change interventions. [14] Personalised nutrition has been defined by Stewart-Knox et al. [15] as "healthy eating advice that is tailored to suit an individual based on their own personal health status, lifestyle and/or genetics''. Dietary and physical activity advice can be personalised by providing information to an individual based on their current dietary or physical activity behaviour, phenotypic or clinical markers of health, or their genetics. [16] The

aim of personalised health advice is to provide an individual with more precise and effective dietary or physical activity advice and to motivate behaviour change. [16]

Several studies have reported favourable effects of genotype-based personalised nutrition advice on dietary and physical activity behaviour. Compared to a control group, participants informed of a risk associated genotype significantly improved fat quality of their diet, [17] reduced sodium intake, [18] were more likely to maintain weight loss [19,20] and were more likely to make health behaviour changes to reduce Alzheimer's disease risk. [21] Conversely, no significant effects on behaviour were reported in response to diabetes risk [22] and a weight loss programme. [23] In the Food4Me study, genotype-based personalised advice led to significantly greater adherence to a Mediterranean diet compared to other levels of personalised advice. [24] However, any level of personalised nutrition advice (including genotype) led to reduced saturated fat intake compared to a control group, [25] but had no effect on folate intake [26] or physical activity. [27] One reason for inconsistency in findings may be related to the populations included within studies. Study participants have ranged from interested volunteers [28] to those with a family history of a disease. [21] Studies have consistently reported that participants with either personal or family history of disease are more willing to undergo genetic testing.[29–31] Therefore, studies that have included an at-risk population may be more likely to observe a change in behaviour.

A number of systematic reviews and meta-analyses have been carried out in the area of personalised communication of disease risk on changes in lifestyle behaviours. [32–36] While an early Cochrane review reported a significant beneficial effect of genetic risk estimates of disease on dietary behaviour change. An updated meta-analysis by Hollands et al. ,[32] which analysed dietary data from seven clinical studies reported little or no significant evidence of

a benefit of DNA-based risk communication on dietary behaviour change, with a standardised mean difference (SMD) of 0.12 (95% CI 0.00 to 0.24, p = 0.05). For physical activity behaviour both reviews reported no effect of DNA-based risk communication,[32,36] the updated review pooled data from six studies investigating physical activity, with a SMD of -0.03 (95% CI -0.13 to 0.08, p = 0.62).[32] The authors concluded that there was a small effect of genetic risk communication on dietary behaviours but their findings did not support the use of DNA-based risk communication to motivate behaviour change. Li et al. [35] investigated studies providing genetic risk testing and communication in relation to obesity, T2DM and CVD on dietary intake and physical activity behaviours. Due to heterogeneity in the dietary outcome measures they did not perform a meta-analysis and they concluded that there was an inconsistent impact of genetic risk on dietary behaviour. Only one study was identified that measured the impact of genetic risk communication on physical activity behaviour and reported no significant effect. More recently, two systematic reviews have been published. Horne et al. [33] did not identify a cause-effect relationship between genetic testing and health behaviours; this review included studies investigating diet and physical activity behaviour as well as smoking. Horne et al. [33] reported that nutrition was the most promising area of behaviour change. Jinnette et al. [34] evaluated the effect of personalised interventions on changes in dietary intake. They concluded that compared to other forms of personalisation there was no evidence of the addition of genetic risk as being superior or more effective in improving diet.

The inconsistent findings reported in individual studies and inconclusive statements from previous meta-analyses and systematic reviews plus recent publications in this research area provide a rationale for a further systematic review and meta-analysis of the literature.

Therefore, the aim of this review is to evaluate the efficacy of genotype-based dietary or physical activity advice on behaviour change to reduce the risk of CVD, T2DM or obesity in the general population and individuals that are at-risk of CVD or T2DM.

Methods

The systematic review and meta-analysis was conducted following guidance from the Cochrane Handbook for Systematic Reviews of Interventions [37] and is reported following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). [38] The protocol was registered with PROSPERO (CRD42021231147).

Eligibility criteria

Studies were eligible for inclusion if they were randomised controlled trials (RCTs) or non-randomised studies on interventions (NRSIs). Participants of eligible studies were adults (aged 18 years and above) from the general population or adults at-risk of T2DM or CVD (such as having a family history, overweight or meeting any of the criteria for metabolic syndrome). Studies were included if they contained a genotype-based dietary and/or physical activity advice intervention that aimed to change dietary and/or physical activity behaviour. The mode of delivery of the intervention could be in person or remote. Eligible studies needed to include a comparator group; this could be a control group which received no advice, general advice or non-gene based personalised advice. In studies with multiple arms, the arm that most clearly isolated the effects of gene-based advice was chosen as the comparator. Only articles published in English were included. Observational studies, animal studies and studies without a control group were excluded as were studies with participants under the age of 18 years or populations diagnosed with CVD or T2DM. Obesity is a risk

factor for both CVD and T2DM; therefore, studies with overweight or obese participants were included within the at-risk inclusion criteria (Table 1).

Information sources

The databases searched were MEDLINE, Embase, PsycINFO and the Cochrane Central Register of Controlled Trials (CENTRAL). Reference lists of included studies and relevant previous systematic reviews were screened for additional eligible studies. Searches were from inception to the search date of 7th January 2022. The search strategy combined relevant keywords and Emtree or MeSH terms to search the themes 'personalised nutrition', 'obesity or type II diabetes or cardiovascular disease' and 'health behaviour'. Themes were combined using the Boolean operator 'AND'. Full search strategies for all databases are presented in Supporting Information.

Selection and data collection process

Records identified by the search strategy were uploaded to Covidence systematic review management software. Duplicates were identified and removed. Title and abstract screening were carried out by two researchers independently according to the inclusion and exclusion criteria. Eligible reports were moved to full text review and were assessed independently by two researchers against inclusion and exclusion criteria. Multiple reviewers worked independently at each stage of screening and any disagreements between reviewers were resolved by consensus. If criteria were met, studies were moved to the data extraction phase. Data extraction was carried out by two reviewers independently using Covidence systematic review management software; any disagreements between

reviewers were resolved by consensus. One author entered the extracted data into Review Manager (RevMan) 5.4 software and that data was checked by another author.

Data items

The primary outcomes are quantified measures of dietary behaviour change and quantified measures of physical activity behaviour change to reduce the risk of CVD, T2DM or obesity. Where more than one dietary or physical activity outcome was reported, the outcome with the greatest relevance to the gene-based advice provided and the strongest evidence of an effect on risk of CVD, T2DM or obesity was selected. Where the same outcome was reported in multiple measures the least subjective measure was selected; for example, if physical activity was measured using an accelerometer and a self-reported questionnaire, the data from the accelerometer was included. Where outcomes were measured at multiple time points the longest time point was selected. Data extracted included: study identification details (sponsorship source, country, corresponding author, study registration) study population (baseline characteristics, inclusion/exclusion criteria, sample size), study design (RCT, NRIS), intervention details, and outcome measures including methods and time points.

Study risk of bias assessment

Risk of bias was assessed using the Risk of Bias 2 (RoB 2) tool. [37] The following domains were considered: (1) bias arising from the randomisation process; (2) bias due to deviations from intended interventions; (3) bias due to missing outcome data; (4) bias in measurement of the outcome; (5) bias in selection of the reported result. Overall risk of bias judgement was "low risk of bias" if all domains were deemed to have low risk of bias. If at least one domain

was deemed to raise some concerns but no domain was deemed to have a high risk of bias the study was judged to "raise some concerns". If at least one domain was deemed to have high risk of bias or multiple domains were deemed to raise some concerns, the study was judged to have "high risk of bias". Risk of bias assessment was carried out by two reviewers independently using Covidence review management software. Multiple reviewers worked independently and any disagreements between reviewers were resolved by consensus.

Effect measures

Effect sizes for each outcome (change in dietary behaviour or change in physical activity behaviour) were summarised as SMD. The SMD was used for both dietary and physical activity outcomes as they were assessed by studies using different scales. The SMD allows the studies to be standardised to a uniform scale so they can be combined. [37] SMD was calculated using change-from-baseline scores.

Synthesis methods

Studies were analysed separately for dietary behaviour change and physical activity behaviour change. Planned sub-group analysis was carried out to compare studies in the general population with studies including at-risk participants. Studies were considered to have at-risk participants if participants were recruited to the study based on a characteristic that increased their risk of T2DM or CVD. Where data was presented separately for participants informed of a risk associated genotype and non-risk associated genotype, additional analysis was carried out to compare between risk and non-risk informed groups. Analysis was also carried out to compare these groups (risk and non-risk informed groups) separately to the comparator group (control group or group that received non-gene-based

personalised advice). Effect sizes were centred on zero, with values greater than zero favouring gene-based advice and less than zero the comparator advice. In studies where a reduction in the outcome measure was beneficial, scores were multiplied by -1. [37]

Authors were contacted for missing information for studies that did not report outcomes as mean change from baseline scores and standard deviations. Where authors were unable to provide missing information, mean change scores and standard deviations were imputed using the standard error, 95% confidence intervals or probability values following methods outlined in the Cochrane handbook. [37] The correlation coefficient between the standard deviations for change as well as for baseline and post-intervention from the Food4Me study [39,40] were used to impute standard deviations for changes from baseline for those studies where data was not available from the author [37]. For one study [41] data was reported as log values. Therefore, for this study the SMD was calculated from the log value as the author was unable to provide the untransformed data. A sensitivity analysis was carried out to compare findings on primary outcomes based on mean change-from-baseline scores compared to post intervention scores.

A meta-analysis of SMD scores was conducted using RevMan 5.4 software and a random effects model was used to pool effect sizes. The random effects model using the inverse variance method was chosen since, although all studies aimed to measure dietary or physical activity behaviour change, the specific behaviour measured and the methods of measurement varied between studies. Therefore, rather than estimating a true-effect estimate as would be seen with a fixed effects model, the mean for a distribution of true effects was estimated. [37] Effect estimates and 95% confidence intervals for each included

study and the overall effect for each comparison are presented as forest plots. Heterogeneity was assessed using χ^2 and quantified using I^2 test. [37]

Certainty assessment

The GRADE approach was used to assess confidence in the body of evidence. The following factors were considered to reduce the quality of evidence: limitations in study design or execution (risk of bias), inconsistency of results, indirectness of evidence, imprecision and publication bias. Outcomes were graded as 'high' (very confident that the true effect lies close to that of the estimate of the effect), 'moderate' (moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different), 'low' (confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect) or 'very low' (very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect). [42] Results of assessment of certainty using the GRADE approach are presented in the summary of findings tables for each outcome.

Results:

Study selection

Overall, 7899 records were screened for inclusion, following the removal of duplicates. A total of 7824 were removed after screening of the title and abstract leaving 75 full-text reports to be reviewed. Fourteen reports from 11 studies met the inclusion criteria (Figure 1). There were two reports identified from the Food4Me study that investigated the effect of gene-based personalised advice on dietary patterns using adherence to the Healthy

Eating Index (HEI) [39] or Mediterranean Diet Score (MDS). [24] The HEI outcome was included in the analysis as it was deemed to be a more universal approach. Mediterranean countries (Spain and Greece) were reported to have significantly higher MDS and although HEI scores tended to be higher in Northern EU countries (UK and Netherlands), these differences were not significant. [43]

Characteristics of included studies

Characteristics of included studies are presented in Table 2. [17,18,27,39–41,44–51] Sample size ranged from 57 participants [50] to 1488 [39]; all studies included male and female participants except Roke et al., [50] which included only female participants. Three studies were conducted in the US, [41,47,48] three in Canada, [18,46,50] two in Finland, [17,49] one in the UK [45] and one recruited from seven European countries. [39] Seven of the included studies recruited participants from the general population. [17,18,39,45,49–51] Four studies were carried out on an at-risk population, two studies recruited overweight participants [41,46] and two recruited participants with an increased risk of CVD. [47,48]

Gene-based dietary and or physical activity advice was described as being provided remotely by six studies, [17,18,39,45,50,51] and four studies provided advice in person. [41,46–48] For one study it was not clear how genotype had been disclosed to the participants in that, although advice was provided online, face-to-face counselling was offered on a voluntary basis. [49] Five studies reported inclusion of behaviour change theory within their intervention. The incorporation of behaviour change techniques were reported in two studies, [39,51] one study reported the incorporation of the Theory of Planned Behaviour, [46] one study included the Extended Parallel Process Model [17] and, one study developed an

action plan for behaviour change. [48] The remaining studies did not explicitly report the use of behaviour change theory in their interventions.

The comparator group from five studies were provided with advice based on general healthy eating or physical activity recommendations. [17,18,46,49,50] Six studies provided advice based on phenotypic, family history or current lifestyle assessment. [39,41,45,47,48,51]

All 11 studies included a self-reported measure of dietary behaviour change. Dietary behaviour was measured using a food frequency questionnaire, [18,39,41,45,50] multiple 24 hour recalls [46] or various brief dietary questionnaires. [17,47–49,51] Seven studies included a measure of physical activity behaviour; three studies included an objective measure of physical activity, [27,45,51] and four studies measured physical activity using a self-reported physical activity questionnaire. [17,41,47,48] Two studies were not able to be included in the meta-analysis as physical activity was reported as the number of participants exercising 'at least 2 times a week'. [17,49] Six studies provided a measure of dietary behaviour separately for risk and non-risk participants. [17,18,25,48–50] Two studies provided a measure of physical activity behaviour separately for risk and non-risk participants. [40,48]

All included studies were RCTs, and four reports from the Food4Me study were included in the analysis. [25,27,39,40] Study duration ranged from 8 weeks [45] to 18 months. [49]

Risk of bias

Two reports were judged to have low risk of bias, [45,51] one report was judged to have high risk of bias due to a lack of information regarding deviations from the intended intervention. [49] The remaining 11 reports were judged to have some concerns, many of

which were due to bias in measurement of the outcome as a consequence of self-reported dietary or physical activity behaviour (Figure 2). [17,18,27,39–41,44–51]

Quality of evidence

The first domain considered was risk of bias, the majority of studies were judged to have 'some concerns', two had low risk of bias and one study had high risk of bias. The main concerns were related to the lack of blinding of participants and outcome assessors to the intervention, in addition to self-reporting of outcome measures. For the dietary behaviour outcome, quality scores were downgraded by one level due to the high risk of bias study [49]; that study did not report physical activity behaviour, so the physical activity outcome was not downgraded for risk of bias. The second domain considered was inconsistency of results, which refers to unexplained heterogeneity. [42] Across analysis, χ^2 was not significant and I^2 ranged from 0% (no between-study heterogeneity) to 50% suggesting moderate variation. [37] Sub-group analysis of healthy and at-risk populations did not explain between-study heterogeneity. Confidence limits of studies were mostly overlapping zero for both outcomes. Therefore, although there was some heterogeneity, quality of evidence was not downgraded within this domain. The indirectness of evidence domain considers whether the participants included in studies, the intervention delivered, and outcomes reported enable the research question to be answered. [42] Although PICO criteria were met, due to the variation between interventions and measurement of outcomes, certainty of evidence was downgraded by one level for both dietary behaviour outcome and physical activity for the indirectness of evidence domain. The imprecision of evidence domain is primarily assessed by considering the 95% confidence intervals of the estimate of effect. [42] The confidence intervals of pooled SMD did not include a meaningful effect for dietary or

physical activity behaviour outcomes. In addition, optimal information size, which refers to the number of participants was considered. The number of participants included in the meta-analysis is adequate for both outcomes. Finally, visual inspection of the funnel plots suggest publication bias was not evident. [42]

Dietary behaviour change

Eleven studies, including 2604 participants assessed dietary behaviour change following gene-based dietary or physical activity advice. [17,18,39,41,45–51] Pooled data from these studies suggest no significant benefit of gene-based dietary or physical activity advice compared to no advice, general advice, or personalised advice without genetics (SMD 0.00, 95% CI -0.11 to 0.11, p = 0.98). Pooled sub-group analysis of studies that recruited participants from an at-risk population (SMD 0.00, 95% CI -0.16 to 0.16, p = 0.99) or general population (SMD 0.01, 95% CI -0.14 to 0.16, p = 0.87) also suggest no significant benefit of gene-based advice compared to no advice, general advice, or personalised advice without genetics. Findings are presented as a forest plot (Figure 3 [17,18,39,41,45–51]) and in a summary of findings table (Table 3). Sensitivity analysis was conducted using SMD of final scores and pooled data also suggest no significant benefit of gene-based advice compared to no advice, general advice, or personalised advice without genetics.

Physical activity behaviour change

Six studies, including 1924 participants, assessed physical activity behaviour change following gene-based dietary or physical activity advice. [27,41,45,47,48,51] Pooled data from these studies suggest no significant benefit of gene-based dietary or physical activity advice compared to no advice, general advice, or personalised advice without genetics (SMD -0.01, 95% CI -0.10 to 0.08, p = 0.88). Pooled sub-group analysis of studies that recruited participants from an at-risk population (SMD 0.07, 95% CI -0.18 to 0.31, p = 0.59) or general population (SMD -0.02, 95% CI -0.13 to 0.10, p = 0.77) also suggest no significant benefit of gene-based advice compared to no advice, general advice, or personalised advice without genetics. Findings are presented as a forest plot (Figure 4 [40,41,45,47,48,51]) and in a summary of findings table (Table 3). Sensitivity analysis was conducted using SMD of final scores, pooled data also suggest no significant benefit of gene-based advice compared to no advice, general advice, or personalised advice without genetics. There were two additional studies included in the systematic review that measured physical activity behaviour change but, due to the way the outcome was reported, they were not able to be included in the meta-analysis. Both studies reported no significant effect. [17,49]

Risk v non-risk genotype

Six studies including 444 participants reported change in dietary behaviour separately for participants informed of a risk associated genotype compared to a non-risk associated genotype. [17,25,47–50] Pooled data from these studies suggest no effect of being informed of a risk associated genotype compared to a non-risk associated genotype in addition to genotype-

based dietary or physical activity advice on dietary behaviour (SMD 0.14, 95% CI -0.06 to 0.33, p = 0.16) (Table 4, Figure 5 [17,18,44,48–50]).

Two studies including 298 participants reported change in physical activity behaviour separately for participants informed of a risk associated genotype compared to a non-risk associated genotype. [40,48] Pooled data from these studies suggest no effect of being informed of a risk associated genotype compared to a non-risk associated genotype in addition to genotype-based dietary or physical activity advice on physical activity behaviour (SMD 0.01, 95% CI -0.24 to 0.25, p= 0.96) (Table 4).

Discussion

Summary of main results

The aim of this systematic review was to evaluate the efficacy of genotype-based dietary or physical activity advice on behaviour change to reduce the risk of CVD, T2DM or obesity in the general population and individuals that are at risk of CVD or T2DM. A meta-analysis of pooled data suggests that genotype-based advice does not affect dietary or physical activity behaviour more than general advice or advice based on lifestyle or phenotypic measures. This finding was consistent in studies that had recruited participants from the general population as well as studies that had recruited participants from populations at-risk of CVD or T2DM.

Quality of the evidence

The outcome measures of dietary and physical activity behaviour were judged to be of 'low' and 'moderate' quality of evidence respectively, due to concerns with risk of bias and indirectness of evidence domains. [42] For risk of bias, the main concerns were related to the lack of blinding of participants and outcome assessors to the intervention, in addition to self-reporting of outcome measures. Blinding participants to the intervention is often not feasible in a lifestyle intervention. [52] Only one study attempted to blind the participants to the intervention by providing the control group with information about risk of age-related macular degeneration. [41] Furthermore, due to the subjective nature of measuring dietary intake and physical activity, in the majority of studies, outcome assessors were the participants themselves. Objective measures of dietary intake are available for few aspects of the diet; furthermore, biochemical measures of nutritional status may not reflect dietary intake and therefore behaviour. [53,54] Finally, concerns have been raised that the RoB 2 tool results in lower ratings of overall risk of bias, compared to the previous Cochrane tool for assessing risk of bias in randomised trials (RoB tool). Consequently, this should be considered when comparing risk of bias assessments from this study to assessments of risk of bias in earlier systematic reviews. [55]

The indirectness of evidence domain considers whether the participants included in studies, the intervention delivered, and outcomes reported enable the research question to be answered. [42] Participants of included studies met the inclusion criteria. All studies included an intervention which incorporated the delivery of gene-based dietary or physical activity advice. However, the way in which advice was delivered varied considerably between studies. Some delivered advice remotely [17,18,39,45,50,51] and some in person, [41,46–48] the extent

of advice varied between studies from written advice to counselling sessions. The way in which gene-based advice is delivered may influence understanding and engagement. Health literacy, genetic literacy and e-health literacy have all been suggested to influence understanding. [56] Furthermore, interpretation of genetic risk was significantly greater when delivered in person compared to remote delivery. [57] Outcome measures particularly for diet also varied between studies. These variations in study design could affect both the effectiveness of the intervention and whether the outcome measure could detect a change in behaviour.

Based on this GRADE assessment when interpreting the findings of this meta-analysis it should be acknowledged that the true effect of gene-based dietary and physical activity advice on dietary behaviour change might be markedly different from the estimated effect. However, for physical activity behaviour the true effect is probably close to the estimated effect.

Gene-based advice for behaviour change

The findings of this meta-analysis supersede the findings from two previous meta-analyses of genotype-based advice on dietary and physical activity behaviour change. Marteau et al. [36] reported a significant benefit of gene-based advice on dietary behaviour from two studies (OR 2.24, 95% CI 1.17 to 4.27) but no significant effect from two studies of physical activity behaviour (OR 1.03, 95% CI 0.59 to 1.80). Hollands et al. [32] reported that analysis of seven studies suggested little or no benefit of gene-based advice on dietary behaviour (SMD 0.12, 95% CI 0.00 to 0.24) and no benefit from six studies of physical activity behaviour (SMD -0.03, 95% CI -0.14 to 0.07). Although the present meta-analysis is focused on dietary and physical activity behaviour change to reduce the risk of obesity, T2DM and CVD, it provides

evidence for no beneficial effect from 11 studies of dietary behaviour (SMD 0.00, 95% CI -0.11 to 0.11) and six studies of physical activity behaviour (SMD -0.01, 95% CI -0.10 to 0.08).

In addition to these meta-analysis, three recent systematic reviews have carried out thematic analysis of the effect of genotype based advice on dietary [34] and physical activity behaviour. [33,35] Of the lifestyle factors reviewed by Horne et al., [33] dietary behaviour change was suggested to be the most promising in response to gene-based advice. Both Li et al. [35] and Jinnette et al. [34] suggest there are benefits to personalisation of advice, but these can be seen with the addition of lifestyle and or phenotypic measures and the addition of genetics does not appear to provide further benefit. Whilst only one study in the present meta-analysis reported a significant difference in dietary behaviour following gene-based advice, the comparator group for this study was provided with general health eating advice. [18] Two additional studies that reported no significant difference between the gene-based group compared to a group provided with phenotypic or lifestyle based advice reported that compared to a control group there was a significant improvement in dietary behaviour. [25,39] Furthermore, two studies that also reported no significant difference in behaviour between groups reported that behaviour significantly improved from baseline measures in both the intervention and comparator groups. [49,50] These findings are in agreement with those of Li et al. [35] and Jinnette et al. [34] that personalisation of advice can increase positive behaviour change, but also highlight the importance of the comparator group chosen for the determination of the benefit of gene-based dietary and physical activity advice on behaviour change. Comparator groups varied between included studies. Some studies compared to a group that received general healthy eating or physical activity advice, [17,18,46,49,50] whereas others more clearly isolated the gene-based component of

personalised advice from other levels of personalisation and the comparator group received advice based on phenotypic, family history or current lifestyle assessment. [39,41,45,47,48,51] It is important to be able to distinguish between different levels of personalisation; dietary and physical activity advice based on current behaviour and phenotypic measures has been provided by health professionals for a long time in order to motivate healthy behaviour change. Whether the addition of genetic risk of disease to this advice can enhance motivation and maintenance of behaviour change is what this meta-analysis aimed to find out. The findings of this meta-analysis and previous reviews would suggest that benefits beyond other levels of personalisation are not observed. However, it is also important to consider that three studies included in the meta-analysis reported no significant difference in behaviour following gene-based advice but more importantly they did not report any significant difference in the comparative or control group either. [17,45,51] Therefore, it is unclear if this lack of an effect on behaviour was due to the gene-based advice. The heterogeneity of interventions delivered, populations and disease context of the included studies may explain the contradictory findings and are discussed below.

Marteau & Weinman [58] suggest that one reason why gene-based advice may not motivate behaviour change is due to a fatalistic attitude towards the disease in those that are informed of a risk-associated genotype. When informed of a phenotypic risk factor such as a high cholesterol level, individuals relate this to their lifestyle (a high intake of saturated fat) and consequently reduce their saturated fat intake. They are less able to draw such links between their genes and cholesterol level and as a consequence are less motivated to make behaviour changes, as they perceive them to be less effective to counteract their genetic predisposition. [58] To avoid this inaccurate interpretation, interventions should choose

genetic predispositions that respond to lifestyle modifications, highlighting how the specific genetic predisposition can be moderated by actionable advice. It is not possible to determine precisely how gene-based advice was delivered in the included studies or indeed how this was perceived by participants, however, this could be a potential source of bias in determining the effectiveness of gene-based advice.

It is important to note that the findings from this meta-analysis suggest that gene-based advice does not cause negative changes in dietary or physical activity behaviour. Those informed of their gene-based risk have a similar response to those in the comparator group. Moreover, within the intervention group there were a proportion of participants informed of a risk associated genotype and a group that were informed of a non-risk genotype. It is also important to consider how these two groups may respond differently to dietary and physical activity advice. One way in which gene-based advice has been proposed to encourage behaviour change is by challenging an individual's optimistic bias, the phenomenon by which an individual underestimates their own risk of developing a disease, such as CVD, compared to others. [13] The disease context of the studies included in this meta-analysis are all polygenic diseases and risk is determined by both genetics and lifestyle behaviours. [9–11,59] Studies have demonstrated how those with a low-risk genotype but an unfavourable lifestyle can be at comparable risk of disease outcomes than those with a high-genetic risk but favourable lifestyle. [60] Consequently, it is equally important that gene-based advice does not enhance poor lifestyle behaviours in those informed of a higher genetic risk due to genetic fatalism [58,61] or in those informed of lower genetic risk by increasing their optimistic bias. [62] To determine the effects of disclosure of a risk associated or non-risk associated genotype, behaviour change between risk and non-risk informed

groups for both dietary and physical activity behaviour was compared. In all six studies that compared dietary behaviour between participants informed of a risk compared to non-risk genotype there was a SMD that favoured the risk informed group; however, this was not statistically significant. In the two studies that reported for physical activity behaviour there was no effect. Similar findings were reported by Hollands et al. [32]

There is considerable heterogeneity between studies researching the effect of gene-based advice on dietary and physical activity behaviour and this has been noted in previous systematic reviews. [33–35] Variations in interventions of the included studies have already been discussed; however, an additional consideration in any intervention designed to change behaviour is the incorporation of behaviour change theory in the design. A consistent criticism of previous studies investigating genotype-based behaviour change is the lack of integration of behaviour change theory. [33,34,63] Five studies included in the present meta-analysis mentioned behaviour change to some extent in the delivery of their intervention. [17,39,46,48,51] The remaining studies did not explicitly report the use of behaviour change theory in their interventions, although it is likely that behaviour change techniques were incorporated to some extent even if they were not identified. For this reason sub-group analysis was not carried out to compare studies that reported the use of behaviour change theory to those that did not. Incorporation of behaviour change theory in genetic-based lifestyle behaviour interventions has been suggested as a way of improving efficacy. [14,33] Therefore, any studies wishing to change behaviour should incorporate behaviour change theory within their intervention design.

To determine the effect of an intervention, the assessment of an appropriate outcome to represent the behaviour addressed by the intervention is required. The variation in methods

and measures of dietary and physical activity behaviour have already been discussed. However, it should be acknowledged also that the assessment of dietary and physical activity outcomes are a considerable challenge. [52,64] It is not clear whether such outcomes can be measured with the necessary degree of accuracy to identify behaviour change as a consequence of the intervention. [52,53] One previous systematic review included physiological and clinical measures such as body weight and blood pressure as outcomes, which can be assessed objectively. [35] The problem with physiological and clinical measures is that it is not possible to determine whether the change in outcome is as consequence of participants changing their behaviour or if the gene-based advice has been more effective due to the gene diet interaction. Consequently, for dietary behaviour outcomes it is difficult to address issues related to self-reporting. A number of studies did measure physical activity behaviour objectively [27,45,51] and subsequent research to assess physical activity behaviour should utilise objective measures.

The aim of personalised health advice is to provide an individual with more precise and effective dietary or physical activity advice and to motivate behaviour change. [16] This and previous meta-analyses suggest that the addition of genetics to personalised advice may not motivate behaviour change beyond that observed at levels of personalisation based on current behaviour or phenotypic measures. [32,34,35] However, in younger populations where unhealthy lifestyle behaviours are yet to develop and phenotypic measures are within the healthy range, personalisation based on genetics may enable the prevention of the development of these behaviours and subsequent phenotypic outcomes. Further research in the use of gene-based personalisation of advice in younger populations is warranted.

Strengths and limitations

Strengths of the present meta-analysis are that guidance from the Cochrane handbook and PRISMA were followed to comprehensively address the study aim. It updates the understanding of the use of gene-based dietary and physical activity advice for behaviour change and included findings from 11 studies. As discussed, the main limitation of the review is the between-study heterogeneity in the delivery of the intervention, the comparator group and assessment of the outcome. The impact of these limitations is discussed above. Where studies had numerous outcomes and follow up times, decisions were made by consensus with regards to inclusion. Alternative outcomes showed a different effect in response to advice in some studies; however, outcomes were chosen based on the context of the gene-based advice and disease prevention. Study duration varied widely, from eight weeks [45] to 18 months, [49] with some studies having multiple follow up points. Health behaviour change requires both initiation and maintenance of change; acquiring the motivation to change behaviour is an important step in the initiation of behaviour change. [65] The longest time point was selected for inclusion in the meta-analysis. Some studies demonstrated significant differences between the intervention and comparator group at earlier time points that were not maintained subsequently; however, for this meta-analysis an estimate of maintenance of behaviour change was preferred. Therefore, if investigating different dietary outcomes or the initiation of behaviour change findings may have differed.

Conclusion

The findings from this meta-analysis suggest that the use of genotype-based advice to promote dietary or physical activity behaviour is not more effective than general advice or advice based on lifestyle or phenotypic measures. This finding was consistent in studies that had recruited participants from the general population as well as studies that had recruited

participants from populations at-risk of CVD or T2DM. Future studies of gene-based advice for changing behaviour should incorporate behaviour change theory explicitly in their design and where possible behaviour outcomes should be measured objectively.

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Supporting Information:

PRISMA checklist S1

Full search strategies for all databases S2

References

1. GBD 2017 Risk Factors Collaborators. Global, regional, and national comparative risk assessment of 84 behavioural, environmental and occupational, and metabolic risks or clusters of risks for 195 countries and territories, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet*. 2018;392(10159):1923-1994. doi:10.1016/S0140-6736(18)32225-6

2. World Health Organisation. *Noncommunicable Diseases Country Profiles 2018*.; 2018.

3. UN General Assembly. *Transforming Our World : The 2030 Agenda for Sustainable Development*.; 2015.

4. Department of Health & Social Care. *Tackling Obesity: Empowering Adults and Children to Live Healthier Lives*.; 2020.

5. Kluge HHP, Wickramasinghe K, Rippin HL, et al. Prevention and control of non-communicable diseases in the COVID-19 response. *The Lancet*. 2020;395(10238):1678-1680. doi:10.1016/S0140-6736(20)31067-9

6. de Gonzalez AB, Hartge P, Cerhan JR, et al. Body-Mass Index and Mortality among 1.46 Million White Adults. *N Engl J Med*. 2010;363(23):2211-2219. doi:10.1056/NEJMoa1000367

7. Singh GM, Danaei G, Farzadfar F, et al. The Age-Specific Quantitative Effects of Metabolic Risk Factors on Cardiovascular Diseases and Diabetes: A Pooled Analysis. *PLOS ONE*. 2013;8(7):e65174. doi:10.1371/journal.pone.0065174

8. Dunkley AJ, Bodicoat DH, Greaves CJ, et al. Diabetes Prevention in the Real World: Effectiveness of Pragmatic Lifestyle Interventions for the Prevention of Type 2 Diabetes and of the Impact of Adherence to Guideline Recommendations: A Systematic Review and Meta-analysis. *Diabetes Care*. 2014;37(4):922-933. doi:10.2337/dc13-2195

9. Hu FB, Manson JE, Stampfer MJ, et al. Diet, lifestyle, and the risk of type 2 diabetes mellitus in women. *N Engl J Med*. 2001;345(11):790-797. doi:10.1056/NEJMoa010492

10. Yusuf S, Hawken S, Ôunpuu S, et al. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. *The Lancet*. 2004;364(9438):937-952. doi:10.1016/S0140-6736(04)17018-9

11. Zheng Y, Manson JE, Yuan C, et al. Associations of Weight Gain From Early to Middle Adulthood With Major Health Outcomes Later in Life. *JAMA*. 2017;318(3):255-272. doi:10.1001/jama.2017.7092

12. Global Nutrition Report. *2021 Global Nutrition Report: The State of Global Nutrition.*; 2021. Accessed June 13, 2022. https://globalnutritionreport.org/reports/2021-global-nutrition-report/

13. Shepherd R. Social determinants of food choice. *Proceedings of the Nutrition Society*. 1999;58(4):807-812. doi:10.1017/S0029665199001093

14. NICE. Overview | Behaviour change: general approaches | Guidance | NICE. Published 2007. Accessed July 10, 2019. https://www.nice.org.uk/Guidance/PH6

15. Stewart-Knox B, Kuznesof S, Robinson J, et al. Factors influencing European consumer uptake of personalised nutrition. Results of a qualitative analysis. *Appetite*. 2013;66:67-74. doi:10.1016/j.appet.2013.03.001

16. Grimaldi KA, van Ommen B, Ordovas JM, et al. Proposed guidelines to evaluate scientific validity and evidence for genotype-based dietary advice. *Genes Nutr*. 2017;12:35. doi:10.1186/s12263-017-0584-0

17. Hietaranta-Luoma HL, Tahvonen R, Iso-Touru T, Puolijoki H, Hopia A. An intervention study of individual, apoE genotype-based dietary and physical-activity advice: impact on health behavior. *J Nutrigenet Nutrigenomics*. 2014;7(3):161-174. doi:10.1159/000371743

18. Nielsen DE, El-Sohemy A. Disclosure of genetic information and change in dietary intake: a randomized controlled trial. *PLoS ONE*. 2014;9(11):e112665. doi:10.1371/journal.pone.0112665

19. Arkadianos I, Valdes AM, Marinos E, Florou A, Gill RD, Grimaldi KA. Improved weight management using genetic information to personalize a calorie controlled diet. *Nutr J*. 2007;6:29. doi:10.1186/1475-2891-6-29

20. Vranceanu M, Pickering C, Filip L, et al. A comparison of a ketogenic diet with a LowGI/nutrigenetic diet over 6 months for weight loss and 18-month follow-up. *BMC Nutr*. 2020;6:53. doi:10.1186/s40795-020-00370-7

21. Chao S, Roberts JS, Marteau TM, Silliman R, Cupples LA, Green RC. Health behavior changes after genetic risk assessment for Alzheimer disease: The REVEAL Study. *Alzheimer Dis Assoc Disord*. 2008;22(1):94-97. doi:10.1097/WAD.0b013e31815a9dcc

22. Grant RW, O'Brien KE, Waxler JL, et al. Personalized genetic risk counseling to motivate diabetes prevention: a randomized trial. *Diabetes Care*. 2013;36(1):13-19. doi:10.2337/dc12-0884

23. Frankwich KA, Egnatios J, Kenyon ML, et al. Differences in Weight Loss Between Persons on Standard Balanced vs Nutrigenetic Diets in a Randomized Controlled Trial. *Clin Gastroenterol Hepatol*. 2015;13(9):1625-1632.e1. doi:10.1016/j.cgh.2015.02.044

24. Livingstone KM, Celis-Morales C, Navas-Carretero S, et al. Effect of an Internet-based, personalized nutrition randomized trial on dietary changes associated with the Mediterranean diet: the Food4Me Study. *Am J Clin Nutr*. 2016;104(2):288-297. doi:10.3945/ajcn.115.129049

25. Fallaize R, Celis-Morales C, Macready A, et al. The effect of the apolipoprotein E genotype on response to personalized dietary advice intervention: findings from the Food4Me randomized controlled trial. 2016;104(3):827-836. doi:10.3945/ajcn.116.135012

26. O'Donovan CB, Walsh MC, Forster H, et al. The impact of MTHFR 677C → T risk knowledge on changes in folate intake: findings from the Food4Me study. *Genes Nutr*. 2016;11:25. doi:10.1186/s12263-016-0539-x

27. Marsaux CF, Celis-Morales C, Fallaize R, et al. Effects of a Web-Based Personalized Intervention on Physical Activity in European Adults: A Randomized Controlled Trial. *J Med Internet Res*. 2015;17(10). doi:10.2196/jmir.4660

28. Celis-Morales C, Livingstone KM, Marsaux CFM, et al. Design and baseline characteristics of the Food4Me study: a web-based randomised controlled trial of personalised nutrition in seven European countries. *Genes Nutr*. 2015;10(1):450. doi:10.1007/s12263-014-0450-2

29. Bayer S, Drabsch T, Schauberger G, Hauner H, Holzapfel C. Knowledge, opinions and expectations of adults concerning personalised genotype-based dietary recommendations: a German survey. *Public Health Nutr*. 2021;24(7):1916-1926. doi:10.1017/S1368980020004152

30. Stewart-Knox BJ, Bunting BP, Gilpin S, et al. Attitudes toward genetic testing and personalised nutrition in a representative sample of European consumers. *Br J Nutr*. 2009;101(7):982-989. doi:10.1017/S0007114508055657

31. Vallée Marcotte B, Cormier H, Garneau V, Robitaille J, Desroches S, Vohl MC. Nutrigenetic Testing for Personalized Nutrition: An Evaluation of Public Perceptions, Attitudes, and Concerns in a Population of French Canadians. *Lifestyle Genom*. 2018;11(3):155-162. doi:10.1159/000499626

32. Hollands GJ, French DP, Griffin SJ, et al. The impact of communicating genetic risks of disease on risk-reducing health behaviour: systematic review with meta-analysis. *BMJ*. 2016;352. doi:10.1136/bmj.i1102

33. Horne J, Madill J, O'Connor C, Shelley J, Gilliland J. A Systematic Review of Genetic Testing and Lifestyle Behaviour Change: Are We Using High-Quality Genetic Interventions and Considering Behaviour Change Theory? *Lifestyle Genomics*. 2018;11(1):49-63. doi:10.1159/000488086

34. Jinnette R, Narita A, Manning B, McNaughton SA, Mathers JC, Livingstone KM. Does Personalized Nutrition Advice Improve Dietary Intake in Healthy Adults? A Systematic Review of Randomized Controlled Trials. *Advances in Nutrition*. 2020;(nmaa144). doi:10.1093/advances/nmaa144

35. Li SX, Ye Z, Whelan K, Truby H. The effect of communicating the genetic risk of cardiometabolic disorders on motivation and actual engagement in preventative lifestyle modification and clinical outcome: a systematic review and meta-analysis of randomised controlled trials. *British Journal of Nutrition*. 2016;116(5):924-934. doi:10.1017/S0007114516002488

36. Marteau TM, French DP, Griffin SJ, et al. Effects of communicating DNA-based disease risk estimates on risk-reducing behaviours. *Cochrane Database Syst Rev*. 2010;(10):CD007275. doi:10.1002/14651858.CD007275.pub2

37. Higgins JP, Thomas J, Chandler J, et al. *Cochrane Handbook for Systematic Reviews of Interventions*. 6.3.; 2022. Accessed February 14, 2022. https://training.cochrane.org/handbook/current

38. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ*. 2021;372:n71. doi:10.1136/bmj.n71

39. Celis-Morales C, Livingstone KM, Marsaux CF, et al. Effect of personalized nutrition on health-related behaviour change: evidence from the Food4Me European randomized controlled trial. *Int J Epidemiol*. 2017;46(2):578-588. doi:10.1093/ije/dyw186

40. Marsaux CF, Celis-Morales C, Livingstone KM, et al. Changes in Physical Activity Following a Genetic-Based Internet-Delivered Personalized Intervention: Randomized Controlled Trial (Food4Me). *J Med Internet Res*. 2016;18(2). doi:10.2196/jmir.5198

41. Voils C, Coffman C, Grubber J, et al. Does Type 2 Diabetes Genetic Testing and Counseling Reduce Modifiable Risk Factors? A Randomized Controlled Trial of Veterans. 2015;30(11):1591-1598. doi:10.1007/s11606-015-3315-5

42. Schünemann H, Brożek J, Guyatt G, Oxman A. GRADE handbook. Published online 2013. Accessed April 10, 2022. https://gdt.gradepro.org/app/handbook/handbook.html

43. Fallaize R, Livingstone KM, Celis-Morales C, et al. Association between Diet-Quality Scores, Adiposity, Total Cholesterol and Markers of Nutritional Status in European Adults: Findings from the Food4Me Study. *Nutrients*. 2018;10(1):E49. doi:10.3390/nu10010049

44. Fallaize R, Celis-Morales C, Macready AL, et al. The effect of the apolipoprotein E genotype on response to personalized dietary advice intervention: findings from the Food4Me randomized controlled trial. *Am J Clin Nutr*. 2016;104(3):827-836. doi:10.3945/ajcn.116.135012

45. Godino JG, van Sluijs EMF, Marteau TM, Sutton S, Sharp SJ, Griffin SJ. Lifestyle Advice Combined with Personalized Estimates of Genetic or Phenotypic Risk of Type 2 Diabetes, and Objectively Measured Physical Activity: A Randomized Controlled Trial. *PLoS Med*. 2016;13(11):e1002185. doi:10.1371/journal.pmed.1002185

46. Horne J, Gilliland J, O'Connor C, Seabrook J, Madill J. Enhanced long-term dietary change and adherence in a nutrigenomics-guided lifestyle intervention compared to a population-based (GLB/DPP) lifestyle intervention for weight management: results from the NOW randomised controlled trial. *BMJ Nutrition, Prevention & Health*. Published online May 21, 2020:bmjnph-2020-000073. doi:10.1136/bmjnph-2020-000073

47. Knowles J, Zarafshar S, Pavlovic A, et al. Impact of a Genetic Risk Score for Coronary Artery Disease on Reducing Cardiovascular Risk: A Pilot Randomized Controlled Study. *Front Cardiovasc Med*. 2017;4:53. doi:10.3389/fcvm.2017.00053

48. Kullo I, Jouni H, Austin E, et al. Incorporating a Genetic Risk Score Into Coronary Heart Disease Risk Estimates: effect on Low-Density Lipoprotein Cholesterol Levels (the MI-GENES Clinical Trial). 2016;133(12):1181-1188. doi:10.1161/CIRCULATIONAHA.115.020109

49. Leskinen HM, Tringham M, Karjalainen H, et al. APOE Genotype Disclosure and Lifestyle Advice in a Randomized Intervention Study with Finnish Participants. *The Journal of Nutrition*. 2021;151(1):85-97. doi:10.1093/jn/nxaa316

50. Roke K, Walton K, Klingel SL, et al. Evaluating Changes in Omega-3 Fatty Acid Intake after Receiving Personal FADS1 Genetic Information: A Randomized Nutrigenetic Intervention. *Nutrients*. 2017;9(3). doi:10.3390/nu9030240

51. Silarova B, Sharp S, Usher-Smith JA, et al. Effect of communicating phenotypic and genetic risk of coronary heart disease alongside web-based lifestyle advice: the INFORM Randomised Controlled Trial. *Heart*. 2019;105(13):982-989. doi:10.1136/heartjnl-2018-314211

52. Mirmiran P, Bahadoran Z, Gaeini Z. Common Limitations and Challenges of Dietary Clinical Trials for Translation into Clinical Practices. *Int J Endocrinol Metab*. 2021;19(3):e108170. doi:10.5812/ijem.108170

53. Laville M, Segrestin B, Alligier M, et al. Evidence-based practice within nutrition: what are the barriers for improving the evidence and how can they be dealt with? *Trials*. 2017;18:425. doi:10.1186/s13063-017-2160-8

54. Margetts BM, Nelson M. *Design Concepts in Nutritional Epidemiology*. OUP Oxford; 1997.

55. Sterne JAC, Savović J, Page MJ, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ*. 2019;366:l4898. doi:10.1136/bmj.l4898

56. Haga SB, Mills R, Pollak KI, et al. Developing patient-friendly genetic and genomic test reports: formats to promote patient engagement and understanding. *Genome Medicine*. 2014;6(7):58. doi:10.1186/s13073-014-0058-6

57. Haga SB, Barry WT, Mills R, et al. Impact of Delivery Models on Understanding Genomic Risk for Type 2 Diabetes. *PHG*. 2014;17(2):95-104. doi:10.1159/000358413

58. Marteau TM, Weinman J. Self-regulation and the behavioural response to DNA risk information: a theoretical analysis and framework for future research. *Soc Sci Med*. 2006;62(6):1360-1368. doi:10.1016/j.socscimed.2005.08.005

59. De Caterina R, Alfredo MJ, Kohlmeier M. *Principles of Nutrigenetics and Nutrigenomics*. Elsevier; 2020. doi:10.1016/C2015-0-01839-1

60. Khera AV, Emdin CA, Drake I, et al. Genetic Risk, Adherence to a Healthy Lifestyle, and Coronary Disease. *New England Journal of Medicine*. 2016;375(24):2349-2358. doi:10.1056/NEJMoa1605086

61. Ehrlinger J, Burnette JL, Park J, Harrold ML, Orvidas K. Incremental theories of weight and healthy eating behavior. *Journal of Applied Social Psychology*. 2017;47(6):320-330. doi:10.1111/jasp.12439

62. Hunter DJ, Khoury MJ, Drazen JM. Letting the Genome out of the Bottle — Will We Get Our Wish? *N Engl J Med*. 2008;358(2):105-107. doi:10.1056/NEJMp0708162

63. French DP, Cameron E, Benton JS, Deaton C, Harvie M. Can Communicating Personalised Disease Risk Promote Healthy Behaviour Change? A Systematic Review of Systematic Reviews. *ann behav med*. 2017;51(5):718-729. doi:10.1007/s12160-017-9895-z

64. Goldberg GR, Black AE, Jebb SA, et al. Critical evaluation of energy intake data using fundamental principles of energy physiology: 1. Derivation of cut-off limits to identify under-recording. *Eur J Clin Nutr*. 1991;45(12):569-581.

65. Ryan RM, Patrick H, Deci EL, Williams GC. Facilitating health behaviour change and its maintenance: Interventions based on Self-Determination Theory. Published online 2008:4.

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Table Legend and Figure Legend

Table 1. PICOS criteria for the inclusion of studies.

Table 2. Study characteristics and reported results included in the meta-analysis.

Table 3. Summary of findings for the main comparison: Dietary and physical activity behaviour change following gene-based dietary or physical activity advice compared to no advice, general advice, or personalised advice without genetics.

Table 4. Summary of findings: Dietary and physical activity behaviour change following gene-based dietary or physical activity advice, participants informed of a risk associated genotype compared to participants informed of a non-risk associated genotype.

Figure 1: PRISMA flow diagram of reports identified and included in the meta-analysis.

Figure 2. Risk of bias judgments for each included study.

Figure 3: Forest plot of main comparison: Dietary behaviour change following gene-based dietary or physical activity advice compared to no advice, general advice or personalised advice without genetics (SMD calculated from diet change from baseline).

Figure 4: Forest plot of main comparison: Physical activity behaviour change following gene-based dietary or physical activity advice compared to no advice, general advice or personalised advice without genetics (SMD calculated from diet change from baseline).

Figure 5: Forest plot of dietary behaviour change following gene-based dietary or physical activity advice, participants informed of a risk associated genotype compared to participants informed of a non-risk associated genotype (SMD calculated from diet change from baseline).

Figure 6: Forest plot of physical activity behaviour change following gene-based dietary or physical activity advice, participants informed of a risk associated genotype compared to participants informed of a non-risk associated genotype (SMD calculated from diet change from baseline).

Table 1. PICOS criteria for the inclusion of studies.

Parameter	Inclusion Criteria	Exclusion Criteria
Participants	Adults General population or at-risk of T2DM or CVD	Participants < 18 years Diagnosed with CVD or T2DM
Interventions	Gene-based dietary and/or physical activity advice intervention that aimed to change dietary and/or physical activity behaviour	Interventions that did not provide dietary and/or physical activity gene-based advice aimed to change dietary and/or physical activity behaviour
Comparisons	Control group which received no advice, general advice or non-gene based personalised advice	Studies without a control or comparator group
Outcomes	Quantified measures of dietary and or physical activity behaviour change to reduce the risk of CVD, T2DM or obesity	
Study Design	RCTs or NRSI	Observational studies, animal studies, reviews.

CVD: cardiovascular disease, NRSI: non-randomised studies on interventions, RCT: randomised controlled trial, T2DM: type 2 diabetes.

Table 2. Study characteristics and reported results included in the meta-analysis.

Study	**Participants** Age Country Population	**Study design** Duration Inclusion of behaviour change theory	**Intervention**	**Comparison**	**Outcomes for review**	**Results**
(Celis-Morales et al., 2017) Report from Food4Me study	1488 M 618 F 870 18-79 years 7 European countries **General population**	RCT 6 months BCT	Personalised dietary advice provided via online interface on the basis of current diet and PA, phenotypic and genotypic data. Based on *FTO, MTHFR, TCF7L2, APOE, FADS1.*	Personalised dietary advice provided via online interface on the basis of current diet and PA and phenotypic data.	**Diet:** Health Eating Index based on self-reported dietary intake from FFQ.	At 6 months there was no significant difference between intervention group and comparator group for HEI. Compared to a control group HEI was significantly greater in participants that received any level of PN.
(Fallaize et al., 2016) Report from Food4Me study	1439 M 611, F 846 40 ± 0.4 years 7 European countries **General population**	RCT 6 months BCT	Personalised dietary advice to reduce SFA intake provided via online interface on the basis of current diet and PA, phenotypic and genotypic data. Based on *APOE*.	Personalised dietary advice to reduce SFA intake provided via online interface on the basis of current diet and PA, phenotypic data.	**Diet:** SFA from self-reported dietary intake from FFQ. **Subgroup-analysis participants informed of genetic risk**	No significant difference in SFA intake between E4+ and E4- participants at 6 months. SFA intake was significantly reduced in participants receiving gene-based advice compared to a control group.
(Godino et al., 2016)	569 M 268 F 301 48.7 ± 7.3 years UK **General population**	RCT 8 weeks BC theory not reported	Standard written lifestyle advice for T2DM, encouraged to maintain a healthy weight and adhere to governmental guidelines for PA and diet. Plus, genetic risk estimate (23 SNPs associated with T2DM)	Standard written lifestyle advice for T2DM, encouraged to maintain a healthy weight and adhere to governmental guidelines for PA and diet. Plus, phenotypic risk estimate (Cambridge Diabetes Risk Score).	**Diet**: Self-reported fruit and vegetable consumption from FFQ. **Physical activity:** Objective energy expenditure.	No significant differences between groups post intervention for physical activity energy expenditure or self-reported fruit and vegetable intake. No significant difference was observed in outcomes compared to a control group.

(Hietaranta-Luoma et al., 2014)	107 M 33, F 74 47.0 ± 12.1 years Finland **General population**	RCT 12 months EPPM	6 communication sessions (lectures on lifestyle and healthy diet, gene-diet interaction*;* health messages and information on personal *ApoE* genotype provided by mail).	6 communication sessions (lectures on lifestyle and healthy diet, gene-diet interaction; common health messages on lifestyle and CVD risk provided by mail)	**Diet**: Self-reported dietary fat quality **Physical activity:** self-reported question leisure time PA. **Subgroup-analysis participants informed of genetic risk**	No significant difference between groups in dietary fat quality or physical activity at 12 months. No significant difference was observed in outcomes compared to a control group.
(Horne et al., 2020)	140 M 18, F 122 Int: 53.5 ± 13.6 years Comp: 56.4 ± 12.1 years Canada **at-risk**: BMI ≥25.0 kg/m^2	RCT 12 months TPB	12-month intervention (weekly meetings for first 3 months then once a month), specific targets derived from genetics for eight nutrients.	12-month intervention (weekly meetings for first 3 months then once a month), specific targets derived from population-based guidelines for eight nutrients.	**Diet:** Self-reported dietary intake of energy.	No significant reduction in energy intake from baseline to 12 months in either group.
(Knowles et al., 2017)	94 Int: M 30 F 19 57±10 years Comp: M 24, F 21 58 ± 8 years US **at-risk**: at least moderate risk CAD	RCT 3 months BC theory not reported	Standard care advice based on phenotypic measures and family history including diet and physical activity to reduce risk of high cholesterol plus GRS for 19 SNPs.	Standard care advice based on phenotypic measures and family history including diet and physical activity to reduce risk of high cholesterol.	**Diet:** Self-reported brief dietary questionnaire. **Physical activity**: Self-reported leisure time PA	No significant difference in diet score or physical activity between groups.
(Kullo et al., 2016)	203 M 97 F 106 59.4 years US **at-risk**: Intermediate risk of CHD	RCT 6 months Action plan for BC	Disclosure of 10-year CHD risk (based on genotype of 28 CHD susceptibility SNPS) by genetic counsellor and visit with physician for shared decision making for statin use. high GRS ≥1.1, low/average GRS ≤1.1.	Disclosure of 10-year CHD risk (based on conventional risk score) by genetic counsellor and visit with physician for shared decision making for statin use.	**Diet:** Self-reported dietary fat intake score. **Physical activity**: self-reported (TAPA) questionnaire. **Subgroup-analysis participants informed of genetic risk**	No significant differences in dietary fat intake or physical activity levels between groups at 6 months.

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(Leskinen et al., 2021)	188 M 33 F 155 51 ± 6 years Finland **General population**	RCT 18 months BC theory not reported	Diet and lifestyle guidance via monthly internet-based lectures, face-to-face counselling, printed education material plus *ApoE* genotype information.	Diet and lifestyle guidance via monthly internet-based lectures, face-to-face counselling, printed education material.	**Diet**: Self-reported dietary fat quality **Physical activity:** self-reported question leisure time PA. **Subgroup-analysis participants informed of genetic risk**	There was no significant difference in fat quality scores or physical activity between groups after 18 months. Fat quality scores were improved in all participants compared to baseline.
(Marsaux et al., 2015) Report from Food4Me study	1480 M 614 F 866 40 ± 13 years 7 European countries **General population**	RCT 6 months BCT	Personalised physical activity advice provided via online interface on the basis of current PAL and BMI, phenotypic (WC and TC) and genotypic data. Based on *FTO*.	Personalised physical activity advice provided via online interface on the basis of current PAL and BMI, phenotypic (WC and TC).	**Physical activity:** Objective measurement of PAL using accelerometer.	No significant difference in activity energy expenditure between groups at 6 months. Significant increase in physical activity from baseline in all groups. No significant difference compared to a control group.
(Marsaux et al., 2016) Report from Food4Me study	1279 M 536, F 743 40 ± 13 years 7 European countries **General population**	RCT 6 months BCT	Personalised physical activity advice provided via online interface on the basis of current PAL and BMI, phenotypic (WC and TC) and genotypic data. Based on *FTO*.	Personalised physical activity advice provided via online interface on the basis of current PAL and BMI, phenotypic (WC and TC).	**Physical activity:** Objective measurement of PAL using accelerometer. **Subgroup-analysis participants informed of genetic risk**	There was no difference in objectively measured physical activity in participants informed of an *FTO* risk genotype or an *FTO* non-risk genotype.
(Nielsen & El-Sohemy, 2014)	138 M 32, F 106 26.5 ± 3.0 years Canada **General population**	RCT 12 months BC theory not reported	Dietary report by email, informed of genotype for *CYP1A2; GSTT1; GTM1; TAS1R2; ACE* and corresponding DNA based recommendation, monthly reminder emailed.	Report of current general recommendations for the same nutrients as intervention with no genetic information.	**Diet:** Self-reported dietary intake of sodium. **Subgroup-analysis participants informed of genetic risk**	Participants in the risk intervention group had a significantly greater reduction in sodium intake compared to the control group at 12-months. No difference between non-risk and control group at 12-months.

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(Roke et al., 2017)	57 F 57 22.0 ± 1.5 years Canada **General population**	RCT 12 weeks BC theory not reported	One-to-one information session. Written general nutritional information about omega-3 FAs and possible health effects Information about effect of *FADS1* (rs174537) SNP on omega-3 FA levels. Letter informing them of *FADS1* genotype.	One-to-one information session. Written general nutritional information about omega-3 FAs and possible health effects. Information about effect of *FADS1* (rs174537) SNP on omega-3 FA levels.	**Diet**: Self-reported omega-3 intake – FFQ. **Subgroup-analysis participants informed of genetic risk**	No significant interaction between group and time. Reported omega 3 intake increased significantly 12 weeks after the intervention in both groups.
(Silarova et al., 2019)	953 M 531, F 422 56.7 years UK **General population**	RCT 12 weeks BCT	Genetic CHD risk estimate (absolute risk of CHD in next 10 years; 'Heart Age' and comparative risk estimate). Web-based lifestyle intervention, 3 interactive sessions delivered at monthly intervals.	Phenotypic CHD risk estimate (absolute risk of CHD in next 10 years; 'Heart Age' and comparative risk estimate). Web-based lifestyle intervention, 3 interactive sessions delivered at monthly intervals.	**Diet:** Self-reported dietary intake of fruit and vegetables **Physical activity:** Objectively measured physical activity – Accelerometer 7 days.	No significant differences in mean change from baseline between groups on objectively measured physical activity. mean change from baseline of self-reported intakes of fruit and vegetables were not significantly different between groups. No significant difference compared to a control group.
(Voils et al., 2015)	601 M 483, F 118 54.1 ± 8.7 years US **at-risk:** baseline BMI ≥ 27 kg/m^2	RCT 6 months. BC theory not reported	T2DM risk counselling session (based on age, race, sex, BMI, family history and FPG) plus genetic risk counselling (based on *TCF7L2, PPARγ, KCNJ11*).	T2DM risk counselling session (based on age, race, sex, BMI, family history and FPG) plus education of age-related macular degeneration.	**Physical activity:** self-reported IPAQ (moderate intensity physical activity). **Diet:** Self-reported energy intake from FFQ	No significant difference in energy intake or physical activity between groups at 6 months.

BC: behaviour change, BCT: behaviour change techniques, BMI: body mass index, CAD: coronary artery disease, CVD: cardiovascular disease, CHD: coronary heart disease, Comp: comparator group, CRS: conventional risk score, EPPM: Extended Parallel Process Model, F: female, FPG: fasting plasma glucose, FA: fatty acid, FFQ: food frequency questionnaire, GRS: genetic risk score, HEI: healthy eating index, Int: Intervention group, M: male, PA: physical activity, PAL: physical activity level, PN: personalised nutrition, RCT: randomised controlled trial, SFA: saturated fat, SNP: single nucleotide polymorphism, TC: total cholesterol, TPB: Theory of Planned Behaviour, T2DM: type 2 diabetes, WC: waist circumference.

Table 3. Summary of findings for the main comparison: Dietary and physical activity behaviour change following gene-based dietary or physical activity advice compared to no advice, general advice, or personalised advice without genetics.

Population: **Adults (general population or at-risk of cardiometabolic disease)** Setting: **Face-to-face or online** Intervention: **genotype-based dietary and/or physical activity advice intervention to change dietary and/or physical activity behaviour** Comparison: **No advice, general advice, or personalised advice without genetics.**			
Outcomes	**Impact:** SMD (95% CI)	**№ of participants (studies)**	**Certainty of the evidence (GRADE)**
Dietary behaviour change: **Self-reported dietary behaviour (24-hour recall, FFQ, other dietary questionnaires)**	No effect of genotype-based dietary or physical activity advice on dietary behaviour for all studies SMD 0.00 (-0.11 – 0.11) or when analysed by sub-group; at-risk SMD 0.00 (-0.16-0.16); general population SMD 0.01 (-0.14 – 0.16).	2604 (11 RCTs)	⨁⨁⨀⨀ Low [a, b]
Physical activity behaviour change: **Objectively measured (accelerometer)** **Self-reported physical activity (various questionnaires)**	No effect of genotype-based dietary or physical activity advice on physical activity behaviour for all studies SMD - 0.01 (-0.10 – 0.08) or when analysed by sub-group; at-risk SMD 0.07 (-0.18-0.31); general population SMD -0.02 (-0.13 – 0.10).	1924 (6 RCTs)	⨁⨁⨁⨀ Moderate [b]

SMD: standardised mean difference; CI: confidence interval; RCT: randomised controlled trial; FFQ: food frequency questionnaire.

[a] Downgraded by one level for high risk of bias: one trial

[b] Downgraded by one level for indirectness: variation between interventions and measurement outcomes

Table 4. Summary of findings: Dietary and physical activity behaviour change following gene-based dietary or physical activity advice, participants informed of a risk associated genotype compared to participants informed of a non-risk associated genotype.

Population: **Adults (general population or at-risk of cardiometabolic disease)** Setting: **Face-to-face or online** Intervention: **Gene-based dietary and/or physical activity advice, participants informed of a risk associated genotype** Comparison: **Gene-based dietary and/or physical activity advice, participants informed of a non-risk associated genotype**			
Outcomes	**Impact:** SMD (95% CI)	**№ of participants (studies)**	**Certainty of the evidence (GRADE)**
Dietary behaviour change: **Self-reported dietary behaviour (FFQ, other dietary questionnaires)**	No effect of being informed of a risk associated genotype compared to a non-risk associated genotype in addition to genotype-based dietary or physical activity advice on dietary behaviour SMD 0.14 (-0.06 – 0.33).	444 (6 RCTs)	⨁⨁⨀⨀ Low [a, b]
Physical activity behaviour change: **Objectively measured (accelerometer)** **Self-reported physical activity (various questionnaires)**	No effect of being informed of a risk associated genotype compared to a non-risk associated genotype in addition to genotype-based dietary or physical activity advice on physical activity behaviour SMD 0.01 (-0.24 – 0.25).	298 (2 RCTs)	⨁⨁⨁⨀ Moderate [b]

SMD: standardised mean difference; CI: confidence interval; RCT: randomised controlled trial; FFQ: food frequency questionnaire.

[a] Downgraded by one level for high risk of bias: one trial

[b] Downgraded by one level for indirectness: variation between interventions and measurement outcomes