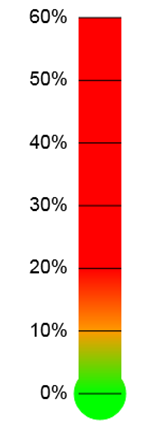
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**S1. Example of phenotypic risk as received by participants**

Originally published in[1].

**Your risk of coronary heart disease based on traditional risk factors**



Risk for a woman with a healthy lifestyle

15%

Your risk

31%

**Your risk now**

Your risk of having coronary heart disease in the next 10 years is 31%. This means that approximately 31 out of 100 women like you (31%) will experience coronary heart disease in the next 10 years.

**Your Heart Age**

Your heart age is 83 years. This means that your risk of having coronary heart disease in the next 10 years is about the same as an 83-year-old woman who does not smoke, does not have diabetes and who has normal blood pressure and cholesterol.

**For comparison,** a woman thesame age as you who does not smoke, exercises regularly, eats healthily and drinks moderate levels of alcohol has a 15% risk of having coronary heart disease during the next 10 years.

**Remember:**

* A high-risk estimate does not mean that you are destined to have coronary heart disease, and a low-risk estimate does not mean that you are completely without risk of having coronary heart disease.
* The estimate we have given you includes the risk of having a fatal or nonfatal coronary heart disease in the next 10 years – for example, angina (chest pain and discomfort on exercise) or a heart attack.
* For most people, there are numerous ways to reduce the risk of having coronary heart disease.

If you would like to know more about the traditional (coronary heart disease) risk estimates please click on the following link (Frequently asked questions):

**Frequently asked questions**

**Where did these estimates come from?**

For people who have not previously had coronary heart disease, the risk of having coronary heart disease can be calculated using published risk estimates (i.e. formulas) that have been developed using large studies, which followed healthy people for more than 10 years, to see who would have coronary heart disease and who would not. Although these estimates apply well to large populations, they do not apply perfectly to all individuals. We used the following information to calculate your traditional coronary heart disease risk estimate:

1. Your age
2. Your sex
3. Your cholesterol level
4. Your HDL (“good”) cholesterol level
5. The information you provided about whether or not you take medication for high blood pressure
6. Your smoking status
7. The information you provided about whether you have diabetes or not

If any of this information is incorrect, the risk estimate might not be accurate.

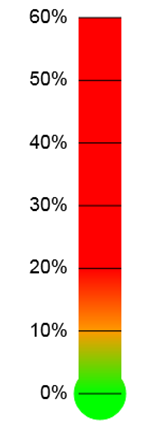
**Why might this risk seem different to what a doctor told me in the past?**

You may have been told in the past that your risk of having coronary heart disease was different than the risk reported here. That may be because we were not able to measure your blood pressure during this study (as a doctor would) and, therefore, had to rely only on the information you provided about whether or not you take medication for high blood pressure. Also there are several different scores used for calculation of coronary heart disease risk estimate.

**S2. Example of genetic risk as received by participants**

Originally published in[1].

**Your risk of coronary heart disease based on genetic factors**

****

Risk for a woman with an optimal genetic risk profile

15%

Your risk

31%

**Your risk now**

Your risk of having coronary heart disease during the next 10 years is 31%. This means that approximately 31 out of 100 women like you (31%) will experience coronary heart disease in the next 10 years.

**Your Heart Age**

Your heart age is 83. This means that your risk of having coronary heart disease in the next 10 years is about the same as an 83-year-old woman who has an optimal genetic risk profile associated with coronary heart disease.

**For comparison,** a woman the same age as you with an optimal genetic risk profile has a 15% risk of having coronary heart disease during the next 10 years.

**Remember:**

* A high-risk estimate does not mean that you are destined to have coronary heart disease, and a low-risk estimate does not mean that you are completely without risk of having coronary heart disease.
* The genetic and coronary heart disease risk estimates are based on different factors, providing you with different information about your coronary heart disease risk. Do not attempt to combine them together to estimate your “total coronary heart disease risk” since this will not be an accurate estimate.
* No matter what the results are from the genetic risk estimate, a key aspect of good heart health remains – follow the advice we have given you regarding improving your diet, doing more exercise and giving up smoking (if applicable).

If you would like to know more about the genetic risk estimates please click on the following link (Frequently asked questions):

**Frequently asked questions**

**How many genes are involved in causing a coronary heart disease?**

For the vast majority of people, we believe that the risk of having coronary heart disease is influenced by many genes (probably hundreds) rather than just one or two.

**What does optimal genetic risk profile mean?**

The optimal genetic risk profile is defined as having less than 10% of the genetic characteristics associated with coronary heart disease.

**How important is family history of coronary heart disease?**

While family history is valuable information, family history not only includes your genetic risk but also your parents’ or siblings’ lifestyle choices, like whether they smoked or not. Based on recent developments in genetics, we are now able to estimate people’s risk much better using genetic information.

NOTE: The answers to frequently asked questions regarding risk estimates are adapted from a randomised trial of personal genomics for preventive cardiology by Knowles et al[2] and from a study by Persell et al.[3].

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**S3. Measures of Secondary outcomes**

Secondary outcomes included: a) objective measures – serum carotenoids (μmol/l, biomarkers for fruit and vegetable intake), total cholesterol (mmol/l), high-density lipoprotein (HDL) cholesterol (mmol/l), low-density lipoprotein (LDL) cholesterol (mmol/l), triglycerides (mmol/l) and fructosamine (μmol/l); b) self-reported measures of anthropometry, diet and lifestyle – weight (kg), fruit intake (servings/day), vegetable intake (servings/day), whole grain intake (servings/day), fish intake (servings/week), alcohol intake (units/week), red and processed meat intake (servings/week), physical activity level (inactive, moderately inactive, moderately active, active), smoking status (yes/no); c) perceived risk – comparative measure, absolute measure, accuracy of risk perception; d) psychological outcomes – overall stress, mood, CHD-related worry. We assessed acceptability of the intervention at 12 weeks post-randomisation by asking participants how much they agreed that the interventions were useful, understandable, trustworthy, motivating and important in helping them decide about CHD risk reduction. Participants provided their answers on five-item Likert scales ranging from “strongly agree” to “strongly disagree”[4].

1. Objective measures

***Serum carotenoids (μmol/l)***: as the measure of dietary behavior through self-report methods is prone to random and systematic measurement error, we included an objective measure of fruit and vegetable intake[5]. We assessed participants’ level of carotenoids before randomisation as part of the two-year follow-up in the INTERVAL study and 12 weeks post-randomisation as part of INFORM study.

***Total cholesterol (mmol/l), high-density lipoprotein (HDL) cholesterol (mmol/l), low-density lipoprotein (LDL) cholesterol (mmol/l), triglycerides (mmol/l) and fructosamine (μmol/l)***: similarly as with serum carotenoids, we obtained these measures at baseline before randomisation (as part of the two-year follow-up in the INTERVAL study) and 12 weeks post-randomisation as part of INFORM study. The blood samples were assessed using standardized procedures by central laboratories.

1. Self-reported measures of anthropometry, diet and lifestyle

***Weight (kg):*** We asked participants to self-report their current weight (in light indoor clothing without shoes) as part of baseline and 12 weeks post-randomisation INFORM questionnaires. We provided them with the option to report their weight in either kilograms or stones/pounds.

***Fruit intake (servings/day), vegetable intake (servings/day), whole grain intake (servings/day), fish intake (servings/week), red and processed meat intake (servings/week)***: We asked participants about their average consumption of fruit and vegetables, whole grains, fish, red and processed meat using simple one-item questions in both baseline and 12 weeks post-randomisation INFORM questionnaires. Those questions reflected the prevention guidelines on CVD[6, 7] at the time of designing INFORM trial. Participants could select answers from a 5-point Likert scale ranging from none to 5+per day/week.

***Alcohol intake (units/week)***: We measured self-reported alcohol consumption as part of baseline and 12 weeks post-randomisation INFORM questionnaires. We asked participants ‘How many units of alcohol do you consume in an average week?’. We provided participants with different examples of what constitutes one unit of alcohol to help them answering the question accurately. The same question was used in the ADDITON-Cambridge trial[8].

***Physical activity level (inactive, moderately inactive, moderately active, active)****:* In addition to objectively measured physical activity (primary outcome), we assessed physical activity subjectively as part of baseline and 12 weeks post-randomisation INFORM questionnaires. We used two questions that referred to physical activity during the past three months. The first question asked about usual physical activity at work, classified into four categories: sedentary, standing (e.g. hairdresser or guard), physical work (e.g. plumber or nurse), and heavy manual work (e.g. construction worker). The second question asked about the amount of time spent, in hours per week, in other physical activities[9].

***Smoking status (yes/no):*** We measured information on participant’s smoking status as part of baseline and 12 weeks post-randomisation INFORM questionnaires. Participants were asked whether they smoke and if yes how much they smoke on an average day (cigarettes, cigars, grams tobacco). In case the participants were ex-smokers, we asked them to indicate in which year they stopped smoking. The same questions were used in the ADDITON-Cambridge trial[8].

1. Perceived risk

***Comparative measure, absolute measure, accuracy of risk perception:*** We assessed participants’ perception of coronary heart disease (CHD) absolute risk using a numerical measure within the time span of 10 years as part of INFORM baseline and 12 weeks post-randomisation questionnaires. We asked participants, ‘On a scale from 0 to 100, where 0 = certain not to happen, and 100 = certain to happen, how likely do you think you are to have coronary heart disease (e.g. heart attack, angina – chest pain and discomfort on exercise) in the next 10 years?’. We also assessed perception of comparative risk as part of INFORM baseline and 12 weeks post-randomisation questionnaires. We asked participants, ‘Compared with other people your age and sex how likely do you think you are to have coronary heart disease (e.g. heart attack, angina – chest pain and discomfort on exercise) in the next 10 years?’. Response options included ‘much less likely than other people’, ‘less likely than other people’, ‘about the same as other people’, ‘more likely than other people’, and ‘much more likely than other people’. These items have been adapted according to recommendations provided by Diefenbach, Weinstein and O’Reilly[10]and have been used in other risk communication studies[11]. We defined accuracy of risk perception as a difference between perception of absolute CHD risk and provided phenotypic CHD risk estimate. For the purpose of this study, we dichotomized accuracy of risk perception into perceived risk > phenotypic risk estimate and perceived risk ≤ phenotypic risk estimate.

1. Psychological outcomes

**Overall stress:** We assessed participants overall level of stress as part of baseline and 12 weeks post-randomisation questionnaires. Similarly, as in the Randomised Trial of Personal Genomics for preventive cardiology by Knowles et al.[2], we asked participants to rate their overall stress level on a 5-item Likert scale ranging from ‘very low’ to ‘very high’.

**Mood:** We measured participants’ mood at baseline and 12 weeks post-randomisation. Two ‘yes’ or ‘no’ questions assessed whether or not the participant has often been bothered by ‘feeling down, depressed or hopeless’ and by ‘little interest or pleasure in doing things’ in the past month (adapted from the Patient Health Questionnaire[12]).

**CHD-related worry:** We assessed the possible negative psychological impact of provision of CHD risk information at 12 weeks post-randomisation. We used adapted Cancer Related Worry Scale (CSW)[13] for the use in the context of CHD as the Coronary Heart Disease Related Worry Scale. The Coronary Heart Disease Related Worry Scale consisted of 6 items that assessed the frequency of worries about having CHD and the impact that these worries have on mood and daily functioning in the past month, e.g., ‘How often do you worry about having coronary heart disease?’ We asked participants to respond to each item on a 4-point response scale. The CSW has been shown to have acceptable test-retest reliability and good internal consistency and has been used in other risk communication trials[11].

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**S4. Examples of questions used in baseline and 12 weeks post randomisation INFORM questionnaires**

**Part: LIFESTYLE**

**WEIGHT**

**How would you prefer to enter your weight?**

* Stones/pounds
* Kilograms

**Please enter your weight**

(without shoes/heavy clothing)

|  |
| --- |
| Kilograms |
|  |

|  |
| --- |
| Stones/pounds |
|  |

**part: DIET**

**For the following questions please tick the box that applies to you the most.**

**How many servings of fruit and vegetables do you consume on an average day?**

(one serving is equivalent to 1 piece of fruit or a standard glass (200mls) of unsweetened juice (only one glass counts); potatoes are not included as a vegetable)

* None
* One a day
* 2–3 per day
* 4 per day
* 5 or more per day

**How many servings of whole grains do you consume on an average day?**

(one serving of whole grain foods includes: wholemeal or whole grain bread (1 slice); wholewheat pasta (2 tablespoons cooked); whole grain breakfast cereal (3 tablespoons) or whole rolled porridge oats (1 tablespoon uncooked).

* None
* One a day
* 2 per day
* 3-4 per day
* 5 or more per day

**How many servings of red meat (beef, lamb, pork, bacon, ham, sausages, and burgers) do you consume during an average week? (one serving is equivalent to 80g, which is approximately the size of a pack of cards; 2 rashers of bacon or 1 ½ standard size sausages)**

**Some average serving sizes of red meat (raw weight): Medium steak = 145g (5.1 oz); Pork chop = 75g (2.6 oz); spaghetti Bolognese with minced beef = 140 g (4.9 oz); serving of roast beef = 90g (3.2 oz)**

* None
* One a week
* 2–3 per week
* 4–6 per week
* 7 or more per week

**How many servings of fish do you consume during an average week?**

(one serving is equal to 140g of cooked fish, or equivalent in size to approximately the size and thickness of the palm of your hand).

* None
* One a week
* 2–4 per week
* 5–6 per week
* 7 or more per week

**part: ALCOHOL**

**How many units of alcohol do you consume in an average week?**

1 unit is equivalent to: ½ pint of beer/cider, 1 glass (125ml) of wine, 1 single measure (25ml) of spirits

|  |  |
| --- | --- |
|  | Units per week |
| Beer/cider |  |
| Wine |  |
| Spirits |  |

**part: PHYSICAL ACTIVITY**

**We would like to know the type and amount of physical activity involved in your work. Please tick what best corresponds to your present occupation from the following possibilities**

|  |  |
| --- | --- |
|  | **Sedentary occupation –** you spend most of your time sitting (e.g. in an office or driving a vehicle) |
|  | **Standing occupation** – you spend most of your time standing or walking. However, your work does not require intense physical effort (e.g. shop assistant, hairdresser, guard, etc.) |
|  | **Manual work** – this involves some physical effort including handling of heavy objects and use of tools (e.g. plumber, electrician, carpenter, etc.) |
|  | **Heavy manual work** – this implies vigorous physical activity including handling of very heavy objects (e.g. docker, miner, bricklayer, construction worker, etc.) |
|  | **I do not work at present** – for example, retired, unemployed, student |

**In a typical week during the past 3 months, how many hours did you spend per week on each of the following activities?**

|  |  |
| --- | --- |
|  | hours per week |
| Walking, including walking to work, shopping and during leisure time |  |
| Cycling, including cycling to work and during leisure time |  |
| Gardening |  |
| Do-it-yourself |  |
| Physical exercise such as keep-fit/aerobics swimming, jogging, tennis, etc. |  |
| Housework such as cleaning, washing, cooking, childcare |  |

**part:** **SMOKING**

**Do you smoke?**

* Yes, daily
* Yes, occasionally (less than one cigarette, cigar or pipe daily)
* No, I have never smoked
* No, but previously I was a smoker.

**I quit smoking in:**

|  |  |
| --- | --- |
|  | Year |
| Please enter the year you quit smoking |  |

**How much do you smoke a day on average?**

* Cigarettes **a day** Number
* Cigars **a day** Number
* Grams tobacco in **a week** Number

**part: YOUR VIEWS ABOUT YOUR RISK OF HAVING CORONARY HEART DISEASE**

**We would like to ask you some questions regarding your views about your risk of having a coronary heart disease (e.g. heart attack, angina – check pain and discomfort on exercise) in the next 10 years. Please read each of the questions below and select the most appropriate value to provide your response.**

**On a scale from 0 to 100, where 0 = certain not to happen, and 100 = certain to happen, how likely do you think you are to have coronary heart disease in the next 10 years?**

|  |  |
| --- | --- |
|  | Value |
| 0 = certain not to happen, 100 = certain to happen |  |

**Compared with other people of your age and sex, how likely do you think you are to have a coronary heart disease in the next 10 years?**

* Much less likely
* Less likely
* About the same
* More likely
* Much more likely

**part: YOUR WELLBEING**

**STRESS**

**How would you rate your overall stress level?**

* Very low
* Low
* Moderate
* High
* Very high
* Prefer not to answer

**MOOD**

**During the past month, have you often been bothered by:**

Feeling down, depressed, or hopeless YES NO

Little interest or pleasure in doing things? YES NO

**part: YOUR THOUGHTS AND FEELINGS ABOUT CORONARY HEART DISEASE (e.g. heart attack, angina – chest pain and discomfort on exercise)**

**We would like to ask you some questions regarding your thoughts and feelings about having coronary heart disease. There are no right or wrong answers. We are most interested in your personal opinion.**

**Please read each of the questions below and tick the most appropriate box to indicate your response.**

**During the past month, how often have you thought about your chances of having a coronary heart disease?**

* not at all or rarely
* sometimes
* often
* almost all the time

**During the past month, how often have thoughts about having a coronary heart disease affected your mood?**

* not at all or rarely
* sometimes
* often
* almost all the time

**During the past month, have thoughts about having a coronary heart disease affected your ability to perform your daily activities?**

* not at all or rarely
* sometimes
* often
* almost all the time

**How concerned are you about the possibility that you may have a coronary heart disease one day?**

* not at all or rarely
* sometimes
* often
* almost all the time

**How often do you worry about having a coronary heart disease?**

* not at all or rarely
* sometimes
* often
* almost all the time

**How much of a problem is worrying about having a coronary heart disease to you?**

* not at all or rarely
* sometimes
* often
* almost all the time

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**S5. Statistical Analysis plan**

Available from[14]

**1 Introduction**

This is the plan for the trial analyses of the primary and secondary outcome variables from a randomised controlled trial to evaluate the effectiveness of providing three different forms of coronary heart disease (CHD) risk information and lifestyle advice on health behaviours. The analyses described in this document will be performed by Stephen Sharp, Senior Statistician, University of Cambridge MRC Epidemiology Unit, once the data have been entered, cleaned and released for use.

This analysis plan refers to the main quantitative outcomes from INFORM. Analyses of data arising from some other quantitative and qualitative components of INFORM will be performed separately by members of the trial team/PhD students/post-doctoral researchers and defined in future analysis plans.

The analyses described in this document are compatible with the recommendations of the CONSORT 2010 statement[15].

**2** **Study outcomes**

**2.1** **Primary outcomes (recorded at baseline and 12 weeks follow-up)**

Objectively measured physical activity (m/s2).

**2.2** **Secondary outcomes (recorded at baseline and 12 weeks follow-up)**

* + 1. Objective measures

Serum carotenoids (μmol/l):

* total.
* alpha-carotene.
* beta-carotene.
* lutein.
* lycopene.
* beta-cryptoxanthin.
* zeaxanthin.

Total cholesterol (mmol/l).

HDL cholesterol (mmol/l).

LDL cholesterol (mmol/l).

Triglycerides (mmol/l).

Fructosamine (μmol/l).

* + 1. Self-reported measures of anthropometry, diet and lifestyle

Weight (kg).

Fruit intake (servings/day).

Vegetable intake (servings/day).

Whole grain intake (servings/day).

Fish intake (servings/week).

Alcohol intake (units/week).

Red and processed meat intake (servings/week).

Physical activity level (inactive, moderately inactive, moderately active, active).

Smoking status (yes/no).

2.2.3 Perceived risk

Comparative measure.

Absolute measure.

Accuracy of risk perception

2.2.4 Psychological outcomes

Overall stress.

Mood.

Coronary heart disease related worry.

**3** **Analysis populations**

All trial analyses will be based on the **Intention To Treat (ITT)** principle, i.e. all participants will be included in the group to which they were randomised, regardless of the intervention actually received.

An analysis of the **primary outcome** will also be performed in a **Per Protocol (PP)** population. Individuals will be included in this population if they accessed risk score and lifestyle information; the precise criteria will be defined based on the distributions of uptake, and applied prior to unblinding of the trial.

**4** **Descriptive analyses**

The following baseline characteristics of the study population will be summarised separately within each randomised group:

Age.

Sex.

Ethnicity.

Marital status.

Socioeconomic status.

Family history of CHD.

History of genetic testing.

History of CHD risk assessment.

Genetic risk related worry/anxiety.

Outcome variables which were measured at baseline will be summarised at baseline and 12 weeks follow-up as described in Section 5.

For continuous variables, means and standard deviations will be presented, unless the variable has a highly skewed distribution, in which case medians, 25th and 75th percentiles will be presented. For categorical variables, the number and percentage of participants within each category will be presented. For each variable (continuous or categorical), the % of missing values will be reported.

No p-values will be calculated for these descriptive analyses.

**5** **Analyses of study outcomes**

**5.1** **Primary outcome**

Change (12 weeks follow-up minus baseline) in the primary outcome, objectively measured physical activity, will be summarised separately in each of the 4 randomised groups using means and standard deviations; the means and standard deviations in each group at baseline and follow-up will also be reported.

Intervention effects will be estimated using analysis of covariance (ANCOVA). The outcome in the ANCOVA model will be change (12 weeks follow-up minus baseline) in physical activity, with the baseline value included as a covariate in the model. An F-test will be performed of the null hypothesis that there is no difference in mean change adjusted for baseline between the 4 randomised groups. The ANCOVA model will also be used to derive estimates of the differences in mean change and 95% confidence intervals for 4 pairwise comparisons defined below:

1. Group 1 (control group) vs. Group 2 (lifestyle advice only) – to estimate the effect of providing lifestyle advice compared with no intervention.
2. Group 3 (phenotypic risk score and lifestyle advice) vs. Group 4 (phenotypic and genetic risk scores and lifestyle advice) – to estimate the effect of providing a genetic risk score in addition to lifestyle advice and a phenotypic risk score.
3. Group 3 + Group 4 vs. Group 1 – to estimate the effect of providing risk score information (phenotypic or genetic or both) and lifestyle advice compared with no intervention.
4. Group 3 + Group 4 vs. Group 2 – to estimate the effect of providing risk score information (phenotypic or genetic or both) in addition to lifestyle advice.

p-values for each of these pairwise comparisons will not be calculated.

An analysis will be performed to check whether adjusting for age (≤60 vs >60) and sex (the randomisation stratifiers) in the ANCOVA model has any impact on the conclusions; if it has no impact, then they will not be included in the model.

**5.2** **Secondary outcomes**

5.2.1 Objective measures

For each outcome, the same analysis will be performed as described in section 5.1. Triglycerides will be log transformed prior to analysis, due to the skewed distribution of this variable.

5.2.2 Self-reported measures of anthropometry, diet and lifestyle

For each continuous outcome, the same analysis will be performed as described in section 5.1. Intakes of fruit, vegetables, whole grain, fish, red and processed meat will all be analysed as continuous variables, derived as described in section 6.1. Physical activity level will also be analysed as a continuous variable with values 0,1,2 and 3.

Smoking status (yes/no) at 12 weeks follow-up will be analysed using a binomial regression model, with adjustment for smoking status at baseline. A likelihood ratio test will be performed of the null hypothesis that there is no difference in risk of smoking adjusted for baseline smoking status between the 4 randomised groups. Estimates of the difference in risk of smoking and 95%confidence intervals for the 4 pairwise comparisons defined in section 5.1 will be derived from this model.

5.2.3 Perceived risk

The comparative measure of risk will be analysed as a continuous variable, coded as follows: much less likely = -2, less likely = -1, about the same = 0, more likely = +1, much more likely = +2. This variable, and the continuous absolute cardiovascular risk (range 0 to 100) will be analysed using the method described in section 5.1.

Accuracy of risk perception will be defined as perceived risk being either ≤ or > the risk estimate, and analysed using a binomial regression model as described for smoking status in section 5.2.2.

5.2.4 Psychological outcomes

Overall stress will be analysed as a continuous variable, coded as follows: very low=1, low=2, moderate=3, high=4, very high=5. This variable, and the continuous mood variable (range 0 to 2), will be analysed using the method described in section 5.1.

Coronary heart disease (CHD) related worry is a continuous variable (range 6-24) only measured at 12 weeks follow-up. Intervention effects will be estimated using linear regression, in which the outcome will be CHD related worry at 12 weeks follow-up. An F-test will be performed of the null hypothesis that there is no difference in mean level of CHD related worry at 12 weeks follow-up between the 4 randomised groups. The model will be used to derive estimates of the differences in mean values of CHD related worry and 95% confidence intervals for the 4 pairwise comparisons defined in section 5.1.

**6** **Considerations for analysis**

**6.1** **Derivation of diet outcomes**

Fruit intake and vegetable intake will each be analysed as number of servings/day, where “None”=0, “One a day”=1, “2-3 per day”=2.5, “4 per day”=4, “5 or more per day”=6.

Whole grain intake will be analysed as number of servings/day, where “None”=0, “One a day”=1, “2 per day”=2, “3-4 per day”=3.5, “5 or more per day”=6.

Fish intake will be analysed as number of servings/week, where “None”=0, “One a week”=1, “2-4 per week”=3, “5-6 per week”=5.5, “7 or more per week”=8.

Red and processed meat intake will be analysed as number of servings/week, where “None”=0, “One a week”=1, “2-3 per week”=2.5, “4-6 per week”=5, “7 or more per week”=8.

**6.2** **Missing data**

*Missing values of primary outcome*

If an individual has a missing value for objectively measured physical activity at follow-up, they will be excluded from the analysis.

The percentage of individuals with missing values of objectively measured physical activity at follow-up will be calculated. Levels of missing data are expected to be low, but if this is not the case, thepotential impact of missing data will be explored in sensitivity analyses using a pattern mixture model[16].

*Missing baseline values of outcomes*

For continuous outcomes, those participants with a missing baseline value of the variable will be included in the analysis using the missing indicator method [17], which is a valid method for pre-randomisation measures in trials, ensuring that no further participants are excluded while maintaining the advantage of improved precision.

**6.3** **Subgroup analyses**

For the primary outcome, the following subgroup analyses will be performed:

1. age (below/above median value).
2. baseline phenotypic coronary heart disease risk score (below/above median value).
3. sex (men/women).
4. BMI (below/above median value).
5. self-perceived risk below/above estimated risk.

For each subgroup analysis, a 3 degrees of freedom F-test of the null hypothesis that there is no interaction between any of the randomised groups and the subgroup variable will be performed. If the p-value for a particular interaction is <0.05, then estimates and 95% confidence intervals for the 4 pairwise comparisons defined in section 5.1 will be derived within each subgroup defined by that particular variable.

**6.4** **Multiplicity**

Given the number of outcomes, randomised groups and therefore comparisons, the results for the primary outcome will be regarded as convincing if the p-value from the 3 d.f. test is <0.01, while the results for each secondary outcome will be regarded as convincing if the relevant p-value from the 3 d.f. test is <0.001.

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**S6. Acknowledgments**

We would like to thank all the participants who agreed to take part in the INFORM trial and made this study possible, and the National Health Service Blood and Transplant of England for collaboration. A complete list of investigators and contributors to the INTERVAL trial is provided in reference[18]. A complete list of investigators and contributors to the INFORM study is provided in reference[1]. Affymetrix (Santa Clara, US) provided genotyping. The MRC Epidemiology Unit Physical Activity Epidemiology Programme [MC\_UU\_12015/3] provided expertise; we are particularly grateful to Tom White MSc (on a PhD scholarship from MedImmune Ltd) from University of Cambridge MRC Epidemiology Unit who processed and interpreted the accelerometer data and provided expertise. We are also grateful to Soren Brage, the Group Leader of the Physical Activity Epidemiology group, University of Cambridge MRC Epidemiology Unit for his help with drafting the text regarding processing of objectively measured physical activity data. UK Biocentre (Stockport, UK) provided laboratory support. Vitas (Oslo, Norway) conducted assays.

**ONLINE SUPPLEMENT**

**S7. Affiliations**

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**ONLINE SUPPLEMENT**

**Table S1.** Baseline demographic and clinical characteristics: differences between those with and without information on the primary outcome

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | **Missing information on physical activity** | | **Nonmissing information on physical activity** | |  |
|  | **N=150** | | **N=803** | |  |
|  | **Total** | **Mean (SD) / % (N)** | **Total** | **Mean (SD) / % (N)** | **p value** |
| Age (yrs) | 150 | 57.2 (8.6) | 803 | 56.6 (8.9) | p=0.4 |
| Sex | 150 |  | 803 |  |  |
| Men |  | 58.7 (88) |  | 55.2 (443) | p=0.4 |
| Women |  | 41.3 (62) |  | 44.8 (360) |  |
| Education | 150 |  | 801 |  | p=0.4 |
| No formal education |  | 0 (0) |  | 1.0 (8) |  |
| Primary education (to age 11 or before) |  | 0.7 (1) |  | 0.2 (2) |  |
| Secondary education (to age 18 or before) |  | 39.3 (59) |  | 42.8 (343) |  |
| University education |  | 60.0 (90) |  | 55.9 (448) |  |
| White | 136 |  | 718 |  | p=0.5 |
| Yes |  | 97.1 (132) |  | 97.9 (703) |  |
| No |  | 2.9 (4) |  | 2.1 (15) |  |
| Family history of CHD | 150 |  | 801 |  | p=0.6 |
| Yes |  | 39.3 (59) |  | 35.7 (286) |  |
| No |  | 54.7 (82) |  | 58.9 (472) |  |
| Don't know/prefer not to answer |  | 6.0 (9) |  | 5.4 (43) |  |
| Phenotypic CHD risk estimate\* | 150 | 5.5 (5.0) | 802 | 5.5 (5.9) | p=0.9 |

\*the estimated absolute risk of having CHD (coronary heart disease) in the next 10 years

Missing information on primary outcome was defined as follows: no data on follow-up physical activity, less than 24 hours recording available for physical activity at baseline or follow-up

**Table S2**. Pairwise comparisons for primary and secondary outcomes – Intention to treat population

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  | **Group 2 vs Group 1** | **Group 4 vs**  **Group 3** | **Groups 3+4 vs**  **Group 1** |  | **Groups 3+4 vs Group 2** |  |  |
|  | **Difference**  **(95% CI)** | **Difference**  **(95% CI)** | **Difference**  **(95% CI)** |  | **Difference**  **(95% CI)** | **p-value** | **N in model** |
| **Primary outcome** |  |  |  |  |  |  |  |
| Physical activity (mg) | 0.09 (-1.15, 1.33) | -0.33 (-1.55, 0.90) | -0.52 (-1.59, 0.55) | | -0.61 (-1.67, 0.46) | 0.592 | 803 |
| **Secondary continuous outcomes** |  |  |  | |  |  |  |
| Serum carotenoids (μmol/l): |  |  |  | |  |  |  |
| Total | 0.11 (-0.04, 0.26) | -0.15 (-0.30, 0.00) | 0.05 (-0.08, 0.18) | | -0.07 (-0.20, 0.07) | 0.117 | 823 |
| Alpha-carotene | 0.01 (-0.01, 0.03) | -0.02 (-0.04, 0.01) | 0.00 (-0.01, 0.02) | | -0.01 (-0.03, 0.01) | 0.332 | 823 |
| Beta-carotene | 0.05 (-0.02, 0.12) | -0.04 (-0.11, 0.03) | -0.01 (-0.07, 0.05) | | -0.05 (-0.11, 0.01) | 0.205 | 823 |
| Lutein | 0.00 (-0.02, 0.02) | 0.00 (-0.02, 0.03) | 0.01 (-0.01, 0.03) | | 0.01 (-0.01, 0.03) | 0.907 | 823 |
| Lycopene | 0.00 (-0.06, 0.06) | -0.05 (-0.11, 0.01) | 0.01 (-0.04, 0.06) | | 0.01 (-0.04, 0.06) | 0.502 | 823 |
| Beta-cryptoxanthin | 0.05 (0.01, 0.09) | -0.04 (-0.09, 0.00) | 0.03 (0.00, 0.07) | | -0.02 (-0.05, 0.02) | 0.018 | 822 |
| Zeaxanthin | 0.00 (0.00, 0.01) | 0.00 (0.00, 0.01) | 0.00 (0.00, 0.01) | | 0.00 (0.00, 0.00) | 0.333 | 822 |
| Total cholesterol (mmol/l) | -0.12 (-0.32, 0.07) | -0.03 (-0.22, 0.17) | -0.05 (-0.22, 0.12) | | 0.07 (-0.10, 0.25) | 0.657 | 823 |
| HDL cholesterol (mmol/l) | 0.02 (-0.05, 0.09) | 0.00 (-0.07, 0.08) | 0.00 (-0.07, 0.06) | | -0.02 (-0.09, 0.04) | 0.895 | 823 |
| LDL cholesterol (mmol/l) | -0.14 (-0.29, 0.00) | -0.05 (-0.20, 0.10) | -0.07 (-0.20, 0.06) | | 0.07 (-0.06, 0.20) | 0.254 | 823 |
| ln-Triglycerides (mmol/l) | -0.05 (-0.12, 0.02) | 0.07 (-0.01, 0.14) | -0.01 (-0.07, 0.05) | | 0.04 (-0.02, 0.10) | 0.127 | 823 |
| Fructosamine (μmol/l) | -1.58 (-8.51, 5.35) | -5.07 (-12.10, 1.95) | 0.62 (-5.38, 6.62) | | 2.22 (-3.83, 8.26) | 0.472 | 823 |
| Weight (kg) | -0.35 (-1.18, 0.48) | 0.54 (-0.33, 1.41) | -0.58 (-1.31, 0.14) | | -0.23 (-0.97, 0.50) | 0.266 | 863 |
| Fruit and vegetable intake (servings/day) | 0.61 (0.39, 0.83) | -0.06 (-0.29, 0.17) | 0.47 (0.28, 0.67) | | -0.14 (-0.33, 0.06) | <0.001 | 861 |
| Whole grain intake (servings/day) | 0.30 (0.07, 0.54) | -0.07 (-0.31, 0.18) | 0.25 (0.05, 0.46) | | -0.05 (-0.26, 0.16) | 0.041 | 861 |
| Fish intake (servings/week) | 0.11 (-0.03, 0.26) | 0.00 (-0.15, 0.15) | 0.16 (0.04, 0.29) | | 0.05 (-0.08, 0.17) | 0.086 | 861 |
| Red and processed meat intake (servings/week) | -0.29 (-0.46, -0.12) | 0.20 (0.03, 0.38) | -0.17 (-0.32, -0.02) | | 0.12 (-0.03, 0.27) | 0.001 | 861 |
| Alcohol intake (units/week) | -0.09 (-1.72, 1.54) | -0.88 (-2.58, 0.82) | -0.12 (-1.54, 1.30) | | -0.03 (-1.47, 1.42) | 0.789 | 861 |
| Physical activity level (4 point scale) | -0.13 (-0.30, 0.05) | -0.13 (-0.31, 0.05) | -0.35 (-0.50, -0.20) | | -0.22 (-0.37, -0.07) | <0.001 | 881 |

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  | **Group 2 vs Group 1** | **Group 4 vs Group 3** | **Groups 3+4 vs**  **Group 1** |  | **Groups 3+4 vs Group 2** |  |  |
|  | **Difference**  **(95% CI)** | **Difference**  **(95% CI)** | **Difference**  **(95% CI)** |  | **Difference**  **(95% CI)** | **p-value** | **N in model** |
| Perceived risk (comparative measure) | 0.03 (-0.09, 0.14) | 0.06 (-0.06, 0.18) | -0.02 (-0.12, 0.09) | | -0.04 (-0.15, 0.06) | 0.674 | 861 |
| Perceived risk (absolute measure) | -0.56 (-8.19, 7.07) | 4.60 (-3.38, 12.59) | -2.69 (-9.34, 3.96) | | -2.13 (-8.90, 4.64) | 0.565 | 861 |
| Overall stress | 0.03 (-0.09, 0.14) | 0.04 (-0.08, 0.16) | 0.01 (-0.09, 0.11) | | -0.02 (-0.12, 0.08) | 0.891 | 858 |
| Mood | -0.06 (-0.14, 0.03) | 0.01 (-0.08, 0.10) | -0.04 (-0.12, 0.03) | | 0.01 (-0.06, 0.09) | 0.557 | 855 |
| CHD-related worry\* | 0.12 (-0.13, 0.37) | -0.28 (-0.54, -0.02) | 0.30 (0.09, 0.52) | | 0.18 (-0.04, 0.40) | 0.006 | 861 |
| **Secondary binary outcomes** |  |  |  | |  |  |  |
| Smoker | -1.83 (-3.88, 0.23) | 0.96 (-1.33, 3.24) | -0.77 (-2.35, 0.80) | | 1.12 (-0.73, 2.97) | 0.288 | 860 |
| Perceived risk > phenotypic risk estimate | 0.47 (-0.10, 1.04) | 0.01 (-0.57, 0.59) | 0.03 (-0.45, 0.51) | | -0.44 (-0.96, 0.08) | 0.347 | 859 |

\* CHD-related worry only measured at 12-week follow-up; difference, 95% CI and p-value estimated from a linear regression model.

NOTE: Group 1: control; Group 2: lifestyle advice only; Group 3: phenotypic risk estimate and lifestyle advice; Group 4: phenotypic and genetic risk estimates and lifestyle advice.

**Primary outcome and secondary continuous outcomes:** Primary outcome and secondary continuous outcomes:Difference (for example, Group 2 minus Group 1) and 95% CI estimated from ANCOVA model with adjustment for baseline.

Participants with missing values of the outcome at baseline included using the missing indicator method.

p-value from a 3 degrees of freedom (d.f.) F-test of the null hypothesis, within an ANCOVA model. Null hypothesis is that there is no difference between the four randomised groups.

**Secondary binary outcomes:** Difference in probability of outcome and 95% confidence interval estimated from binomial regression model, adjusted for baseline value of the outcome.

p-value from a Wald test (3 d.f.) of the null hypothesis that there is no difference in probability of the outcome, adjusted for baseline value of the outcome, between the four randomised groups.

Pre-defined Analysis Plan: Given the number of outcomes, randomised groups and therefore comparisons, the results for the primary outcome will be regarded as convincing if the p-value from the 3 d.f. test is <0.01, while the results for each secondary outcome will be regarded as convincing if the relevant p-value from the 3 d.f. test is <0.001.

**Interpretation:**

*Primary outcome:* There was no evidence of intervention effects on physical activity defined as an average acceleration (mg) over the observation period (difference in adjusted mean change from baseline): lifestyle group vs control group 0.09 mg (95% CI -1.15 to 1.33); genetic group vs phenotypic group -0.33 mg (-1.55 to 0.90); phenotypic group and genetic group vs control group -0.52 mg (-1.59 to 0.55) and vs lifestyle group -0.61 mg (-1.67 to 0.46) (Figure 2; Supplementary material, Table S2 and Table 2). Pre-specified analyses showed that the interventions also had no effect on physical activity within subgroups defined by age (below/above median; p=0.30), sex (men/women; p=0.51), baseline phenotypic CHD risk estimate (below/above median; p=0.87), perceived phenotypic risk below/above absolute risk; p=0.563 and perceived genetic risk below/above absolute risk; p=0.283. The number of participants who completed the intervention per protocol was 120 for the lifestyle advice group (Group 2), 135 for the phenotypic risk group (Group 3), and 117 for the phenotypic and genetic risk group (Group 4). There was no difference in intervention adherence between active intervention arms (p=0.2). For each pairwise comparison, results of the per protocol analysis for the primary outcome were similar in size and direction as the intention to treat analysis.

*Secondary outcomes*: Self-reported fruit and vegetable intake and self-reported physical activity were both statistically significantly different across the groups at the pre-specified threshold of p<0.001. For self-reported fruit and vegetable intake this was driven by an increase in intake following provision of lifestyle advice, with or without risk information: lifestyle group vs control group 0.61 servings/day (0.39 to 0.83); phenotypic group and genetic group vs control group 0.47 servings/day (0.28 to 0.67). The provision of either genetic and/or phenotypic risk information in addition to lifestyle advice or genetic risk information in addition to phenotypic risk was not associated with change: phenotypic and genetic group vs lifestyle group (-0.14 (-0.33 to 0.06); genetic group vs phenotypic group -0.06 (-0.29 to 0.17). By contrast, the difference in self-report physical activity was driven by a reduction in physical activity in those groups receiving either phenotypic or genetic risk information: phenotypic group and genetic group vs control group -0.35 (-0.50 to -0.20); phenotypic group and genetic group vs lifestyle group -0.22 (-0.37 to -0.07). As with self-reported fruit and vegetable intake, the addition of genetic risk information to phenotypic risk was not associated with change: phenotypic group vs genetic group -0.13 (-0.31 to 0.05) (Figure 2; Supplementary material, Table S2 and Table 2).

Although not reaching our pre-defined threshold for statistical significance, CHD-related worry and self-reported red and processed meat intake had p values <0.01. For CHD-related worry this was driven by higher levels of worry in the group that received genetic and/or phenotypic risk compared to the control group (phenotypic group and genetic group vs control group 0.30 (0.09 to 0.52)) and lower levels of worry in the genetic group compared to the phenotypic group (genetic group vs phenotypic -0.28 (-0.54 to -0.02)). For red and processed meat consumption the pattern was similar to self-reported fruit and vegetable intake with provision of lifestyle advice, with or without risk information, associated with a decrease in red and processed meat consumption: lifestyle group vs control group -0.29 servings/day (-0.46 to -0.12); phenotypic group and genetic group vs control group -0.17 servings/day (-0.32 to -0.02). The addition of genetic and/or phenotypic risk to lifestyle advice was not associated with change (phenotypic group and genetic group vs lifestyle group 0.12 (-0.03 to 0.27) while addition of genetic risk information to phenotypic risk was associated with an increased consumption of red and processed meat (genetic group vs phenotypic group 0.20 (0.03 to 0.38).

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