Title: To evaluate the effects of personalized dietary advice on improving diet quality and cardiometabolic health

Aim:

To evaluate the effects of personalised dietary advice, tailored to both individual biomarker profiles and a diet quality assessment (assessed using PDQS questionnaire), on improving diet quality and cardiometabolic health, compared with conventional dietary advice, in adults at risk of cardiovascular disease (CVD) on the island of Ireland. These objectives will be assessed in an adult population who are overweight, consume a poor quality diet and who have one or more other risk factors for CVD, on the island of Ireland. This will be a dual-centre study completed at both Queen's University Belfast and University College Dublin. Ethical approval will be obtained separately through the two institutions to cover each recruitment site.

Objectives:

Conduct a 6-month randomized trial among participants at risk of cardiovascular disease (CVD) living in Northern Ireland to examine the effects of a dietary intervention, tailored to both individuals' food biomarker profiles and a diet quality assessment (assessed using PDQS questionnaire) compared with conventional dietary advice.

- ***Primary outcome***: change in overall diet quality assessed using the Prime Diet Quality Score (PDQS)
- ***Secondary outcomes*****:** cardiometabolic outcomes (i.e., blood pressure, lipid profile and metabolic markers (e.g. HbA1c), and body composition and body weight), change in biomarkers of diet quality, physical activity levels, habitual dietary intake and demographic/lifestyle information.
- ***Exploratory outcome*****:** changes in gut microbiota compositions and functionality.

Background

A healthy dietary pattern, in which saturated fat, sugar and salt are within recommended ranges and intake of fibre, fruit and vegetables is high, is known to reduce the risk of non-communicable diseases (NCDs)[1-5]. However, global burden of NCDs has continued to rise in recent decades, with

71% of worldwide deaths attributable to NCDs[6]. It is thought that up to 80% of cardiovascular diseases and over one third of cancers could be prevented by modifying behaviours such as smoking, diet, alcohol consumption and physical activity[7]. As cardiovascular diseases account for the majority of NCD deaths, more must be done to determine how best to encourage populations to adopt and maintain healthy behaviours to reduce risk of CVD incidence and improve outcomes.

In the context of these rising rates of NCDs, the effectiveness of a personalised nutrition approach has been examined in recent years. Promising evidence from a European dietary intervention has suggested that personalised dietary advice, based on individual baseline diet assessed via food frequency questionnaire, is more effective than conventional dietary advice in producing positive changes in dietary behaviour[8]. Interestingly, in this trial, it was reported that the inclusion of phenotypic or phenotypic plus genotypic information in the generation of personalised dietary advice did not enhance the effectiveness of the intervention when compared with advice based on individual dietary data alone[8].

Although the research in this area is promising, the use of dietary data to tailor personalised dietary advice is limited by the self-reported nature of these methodologies and the substantial measurement error associated with food frequency questionnaires, 24-hour recalls and food diaries[9]. Food biomarkers are, however, able to objectively assess diet without reliance on self-reported dietary intake and although further research is needed to discover, validate and examine novel biomarkers for foods and/or food groups, it is an area of significant potential in the area of personalised nutrition.

The aim of the current project is to examine whether novel food biomarkers, in combination with a diet quality assessment (measured using PDQS questionnaire), can be used to deliver precision nutrition advice and substantially improve cardiometabolic health. This idea is supported by research previously conducted by the research team[10] and will be evaluated for the first time in this trial.

Plan of Investigation

Participants

In total n=134 participants will be recruited, n=85 will be recruited by a research team at Queen's University Belfast. 49 participants will be recruited in UCD.

Population characteristics: Participants who are 18 years or over, overweight, consume a poor quality diet and have one or more other risk factors for cardiovascular disease. Recruitment will take place over a 12-month period.

Participants will be considered eligible to enrol in the study if they are:

- ≥18 years **AND**
- Overweight or obese (BMI >25 kg/m^2 and <45 kg/m^2) **AND**
- have a low diet quality assessed using Prime Diet Quality Score (PDQS) (≤21) **AND** one or more of the following risk factors for CVD:
    - current smoker
    - hypertension (whether pharmacologically managed or not)
    - hypercholesterolaemia (whether pharmacologically managed or not)

***Exclusion criteria*:**

Participants will be ineligible to enrol in the study if they have:

- established CVD (i.e. MI, angina, heart failure, stroke, TIA, peripheral arterial disease or aortic disease)
- a medical condition which would substantially limit ability to complete study requirements (i.e. follow dietary advice and attend study site for data collection).
- following a medically prescribed diet or have a dietary restriction(s) that would substantially limit ability to complete study requirements (e.g. following a diet for management of Type 1 or Type 2 diabetes, weight loss, Coeliac Disease, Inflammatory Bowel Disease, food allergies or any other condition requiring significant dietary management).
- excessive alcohol consumption (>28 units/week for men or >21 units/week for women)
- currently pregnant
- no internet/email access (as this would impact on intervention delivery).
- unable to provide informed consent.

Recruitment

Participants will be recruited from the general population via established recruitment mechanisms. An electronic recruitment poster,email, and/or flyers will be circulated to workplaces and online notification systems e.g. church online bulletins, local online newspapers, online community notices (e.g. University of the Third Age) and social media outlets such as Twitter, Facebook and Instagram. A pop-up banner of the recruitment poster will also be produced and placed in entrance halls of public spaces/workplaces with appropriate permissions obtained. Contact details of the research team will be published on all study advertisements. Managerial permission will be obtained, where relevant, before any online advertisements are circulated or placed within workplace spaces. Recruitment will take place over a 12-month period.

The Belfast site will recruit n=85 participants according to the inclusion and exclusion criteria. The UCD site will recruit 49 participants.

Those who are interested in taking part in the study after reading the study advertisement will be directed to make contact with the research team. The initial screening process will involve asking participants to complete a screening questionnaire (incorporating all aspects of inclusion/exclusion criteria and collection of contact details) via telephone with the researcher. The screening process will rely on self-reported information obtained from the participant and should take approximately 20-30 minutes to complete. After the telephone call, researchers will review responses within the screening questionnaire and email a link to the Participant Information Sheet to those identified as potentially eligible to take part.

After being given at least 48 hours to read the Participant Information Sheet, the researcher will telephone the participant to discuss the research in further detail and ensure the participant fully understands the study information, implications of involvement and answer any questions they might have. If the participant agrees to participate, they will be invited to complete their consent online and attend the Centre for Public Health for baseline data collection.

Study design and assessments

This is a single-blind randomised controlled parallel group dietary intervention, conducted over 6 months in participants at high risk of cardiovascular disease living on the island of Ireland, to evaluate the efficacy of personalised dietary advice, based on both food biomarkers and a diet quality assessment, in improving diet quality and cardiometabolic outcomes.

Study randomisation will be conducted centrally for both sites (Northern Ireland and Republic of Ireland). Once participants have completed their baseline visit, they will be randomized (randomization scheme generated using www.randomization.com with random block sizes) to either control or intervention group. Participants will be stratified by gender and diet quality. Participants will be unaware of which group they have been randomised to. Control participants will be offered personalised dietary advice at the end of the intervention:

1) ***Control*** – participants will be given conventional dietary advice based on current regional population dietary recommendations via email to encourage dietary change towards a better quality diet. Participants will be given the dietary advice at baseline (4 messages) and month 3 (4 messages) of the intervention. Control participants will be offered personalised dietary advice at the end of the intervention.

2) ***Personalized dietary advice*** – participants will be encouraged to make dietary change using individualized recommendations incorporating both food biomarkers and diet quality assessment

(assessed using PDQS questionnaire). Based on these biomarker data and the diet quality assessment, a system of categorization will be developed and decision trees created to ensure standardized delivery of advice within this intervention arm. In this way, the intervention will be standardised across sites. Relevant behaviour change techniques (BCT), i.e. the BCT framework and the CALOR-E diet and physical activity-specific taxonomy[11,12] have been integrated into the intervention development. Dietary advice will be delivered via email in both groups.

Participants will commence on the intervention within one month of their baseline visit. This will enable researchers to collect, process and analyse urine samples to help inform the dietary advice given as part of the intervention.

Dietary advice will be delivered via email. Both groups will receive dietary advice at baseline and month 3. Both groups will receive contact from the research team at months 0, 1, 3 and 6 months via email. The control group will be offered personalised dietary advice at the end of the intervention. As such, the frequency and duration of contact will be similar in both groups.

Outcome measures:

Outcomes will be assessed during a study visit at 0, 3, and 6 months and maintenance data will be collected online at 12 months for the primary outcome.

Primary outcome:

- Change in dietary quality assessed by Prime Diet Quality Score (PDQS). This will also be assessed six months after the intervention completes, to determine whether the intervention influences longer term adherence to a better quality diet. (assessed at 0, 3, 6 and 12 months. The 12 month PDQS (6 months post intervention) will be collected online).

Secondary Outcomes:

1. Change in markers of cardiometabolic risk including:
    - Blood pressure (measured twice from the non-dominant arm, using automated Omron sphygmomanometer, with the participant sitting quietly for at least five minutes. (assessed at 0, 3 and 6 months).

- Lipid profile (fasting blood samples will be drawn from the antecubital vein and immediately separated into plasma/serum for the proposed assays detailed below. It will be stored at -70°C until analysis (assessed at 0, 3 and 6 months).
- Other metabolic markers (e.g. HbA1c) (blood sample as above) (assessed at 0, 3 and 6 months).
- Anthropometric measurements (weight (kg), height (m), measured using calibrated scales and stadiometer, respectively, BMI (kg/m^2), waist and hip circumference and body composition measured by bioelectrical impedance (Bodystat 1500) (assessed at 0, 3 and 6 months)

2. Demographic/lifestyle information (e.g. alcohol consumption, medication use assessed via questionnaire) (assessed at 0 months; shortened change in medication/lifestyle questionnaire administered at 3 and 6 months).
3. Change in biomarkers of diet quality, including food biomarker-based diet quality score (fasting morning urine sample stored at -70ºC until analysis; further details below) (assessed at 0, 3 and 6 months).
4. Physical activity using a 7-day pedometer and Global Physical Activity Questionnaire (GPAQ) (assessed at 0, 3 and 6 months).
5. Habitual dietary intake assessed using the EPIC Food Frequency Questionnaire (assessed at 0, 3 and 6 months).

   All questionnaires will be administered via the online survey software Qualtrics.

Exploratory outcome:

- Gut microbiota composition and functionality. Faecal samples will be collected from participants who consent to contribute to this optional element of the study for exploratory analyses. As faecal samples are required from a large proportion (n=70; n=35 in each study arm) of the n=85 participants we intend to recruit at the QUB site, all participants recruited at QUB will be asked to consider consenting to the provision of faecal samples). Participants will be given a faecal sample home collection kit and instructed to collect a sample during the week following the month 0 and month 6 study visits. Full instructions and a postage box will be provided within the faecal sample collection kit so participants can easily return sample to researchers via post.

Laboratory methodology

All methods utilised are routinely used in the participating laboratories and are performed with careful attention to quality control and with participation in external quality control schemes where available. All laboratory analyses will be conducted blind, i.e., the analyst will not know to which intervention the participant has been assigned.

Biomarkers of cardiometabolic risk:

Serum lipids (total cholesterol, HDL-C, and TG) whole blood HbA1c will be assessed by enzymatic assays (Randox Ltd, Crumlin, NI and Glen Bio, Antrim, NI) on a Randox auto-analysern I-Lab 600 auto-analyzer. LDL-C will be calculated.

Biomarkers of diet quality:

The following biomarkers will be used :

- red meat (methylhistidinescarnosine)
- white meat (guanidoacetate, anserine)
- fruit and vegetables (proline betaine, isothiocyanates, S-methyl-L-cysteine sulfoxide, and tartaric acid)
- wholegrains (alkylresorcinols)
- coffee (phenolic acids, N-methylpyridinium, trigonelline, 2-furoylglycine; SSBs --formate, citrulline, taurine, and isocitrate)
- fish (omega-3 index (20:5n-3 and 22:6n-3; % of total fatty acids).

Others will be added as they emerge in the literature.

Gut microbiome composition and functionality (exploratory):

Faecal samples will be collected via home collection kits, posted back to researchers and stored at Queen's University Belfast in preparation for shipment to US partner laboratories for analyses.

Power

Based on published US data, with a standard deviation (SD) of PDQS of 2.3, as previously seen[13], and an assumption of a difference in increase in PDQS of 5 between the personalized dietary advice and control groups, then, if we have 60 participants in each group, the study would have over 90% power to detect this difference in mean PDQS as statistically significant, at the α=0.05 level. We will recruit 134 participants in total to allow for approximately 10% drop-out. For the health outcomes, and, based on what was observed in a dietary intervention study on improving diet quality in similar, high CVD risk participants[14], if we have 60 participants in each group, and we assume that (i) the SD of the change in diastolic blood pressure (DBP) is 9 mmHg at the end of the study; (ii) a difference in DBP of 4.5 mmHg between the personalized dietary advice and control groups; then the study would have 80% power to detect, as statistically significant at the 5% level, these differences in mean change between the two groups. We will have similar levels of power (~80%) to detect effect sizes of similar magnitude in total cholesterol, HbA1c, and body weight. The analysis of gut microbiota composition and functionality will be exploratory in nature.

Statistical analysis

The repeated end-point measures generated by the study design will be analyzed with techniques appropriate for longitudinal data using the xt panel study procedures available in Stata release 11 (College Station, TX). Initial examination of the correlation structure of the repeated measures will help guide model fitting. The influence of the dietary intervention under study will be assessed by comparing the means of changes in measurements from baseline to 6 months between the personalised dietary advice and control groups. This difference in means will provide an estimate of the effect of intervention and 95% confidence limits will be calculated to indicate its precision. If appropriate, measurements will be logarithmically transformed prior to analysis and interpretation will be made in ratio terms on the original scale. Compositional analysis of whole metagenome and metatranscriptome datasets will be performed using the read-based bioinformatics analysis suite, including the HUMAnN2158 analysis network[15], MetaPhlAn2 profiler[16] and KneadDATA pipeline, developed in the Huttenhower laboratory at Harvard T.H. Chan School of Public Health. Testing for differences in microbial features between intervention and control groups will be performed with the MaAsLin sparse regression method[17]. It is unknown whether men and women respond differently to the same diet, in terms of food biomarker profiles and CHD risk. In previous cohort studies conducted by the research teams, similar associations of various diet quality indices were observed with risk of chronic diseases between men and women[18-21]. In the current study, we consider both men and women, and whenever appropriate, we will perform gender-specific analyses to assess gender difference. We will combine the data of men and women when the test for interactions by gender is not significant, and gender will be adjusted as a covariate.

Process Evaluation

A process evaluation will be conducted at the end of the 6-month study to help elucidate if, how and why the intervention worked. A process evaluation framework for the PAD-Q trial has been developed based on both the Medical Research Council guidance[22] and RE-AIM framework[23].

A large proportion of data for process evaluation will be naturally collected as part of the trial process (receipt of delivery of dietary reports, number of participants making contact with the research team to ask further questions) but to address the outstanding aspects, the research team has developed a brief process evaluation questionnaire (to be administered online) and a guide for a semi-structured follow-up interview to be conducted via telephone. These additional aspects of data collection are optional and will therefore involve a separate Participant Information Sheet and Consent From. The purpose of the online questionnaire is to collect data from participants on intervention fidelity, dose, acceptability, reach, context, mechanisms of impact and contamination, as per MRC framework. In order to allow participants to elaborate further on the aspects reported within the questionnaire, a follow-up phone call will also be an option, which would be expected to last approximately 30 minutes. The phone call will be conducted by a researcher and audio tape-recorded to enable transcription for subsequent analyses. Participants will be reminded that the data collection process will be fully anonymized and that they have the option to ask the research to omit any aspects of the conversation which they do not wish to be transcribed at the end of the phone call.

In order to collect these data, we plan to circulate an email to all participants (both those randomized to the invention or control groups) at the end of the 6-month trial with an Information Sheet attached, specific to process evaluation, to gauge interest in completing the optional process evaluation questionnaire or follow-up phone-call. If a participant expresses interest, researchers will email a link to an electronic consent form. Once consent is completed, researchers will then circulate a link to the process evaluation questionnaire (via Qualtrics survey software) and arrange a follow-up phone call to those who provide consent. Participants will be offered the option to complete either the questionnaire or phone call, or both.

Project timetable, including who will carry out which parts of the project

June 2021-September 2021

Project planning, preparation of study documentation, intervention delivery preparation, development of personalised messaging templates and logistical organisation will be carried out by a Research Fellow and PhD student.

September 2021-September 2023

The recruitment period is expected to last 12 months and commence in September 2021. It is expected that recruitment, randomisation, intervention delivery and data collection will be implemented on a rolling basis between Belfast and Dublin sites. The intervention will be 6 months in duration and the primary outcome will also be collected 6 months post-intervention to determine maintenance. The day-to-day management of the study and all data collection procedures will be undertaken by a Research Fellow and a PhD student.

September 2023-May 2024

Project data analyses, write-up and dissemination.

Data protection issues

Data collected in association with this study will be pseudonymised. Consent and online questionnaire data will be pseudonymised and stored within password-protected databases within secure university OneDrive servers. Only researchers will have access to these data.. All biological samples collected will be pseudonymised and stored within secure -80^{o}C freezers at Queen's University Belfast site. Urine samples will be shipped to University College Dublin for analyses and a Material Transfer Agreement will be in place. Faecal samples, which are an optional element of the study, will be stored at Queen's University Belfast and shipped to partner laboratory in United States for analyses and a Material Transfer Agreement will be in place. Study measurement records (height, height, blood pressure) completed at study visits will be the only hard copy data collected and will be pseudonymised and stored within lockable researcher filing cabinets within the Centre for Public Health. Data will be made available for secondary research in a timely and responsible manner following requests made to and approved by the study research team.

Ethical issues and safety

Participants will be fully informed about the requirements of the study before they provide consent. If a participant feels uncomfortable about providing any of the information, they can withdraw at any time without giving a reason. This trial involves promotion of healthy behaviours tailored to an individual's biomarker profile, where indicated. These purposeful changes in behaviour are healthy behaviours and therefore intended to be of benefit to the participant in terms of their health. Control group participants will be offered the personalised feedback at the end of the intervention.

Biological samples collected as part of this study will not be used in future research unless specific consent is obtained and this is clearly outlined within the Participant Information Sheet. All biological samples will be collected, handled and stored in accordance with Human Tissue Act 2004, where relevant e.g. HcA1C sample; whereby all relevant documentation with regards to the Human Tissue Authority will be in place.

Participants will be informed that if, during the process of data collection, any incidental findings with regards to health (newly concerning lipid profile, HbA1C outside of the normal range, elevated blood pressure measurement) are identified, participants will be informed. Specific consent with regards to contacting the participant's General Practitioner in these instances will be obtained. •

With regards to HbA1C, people previously diagnosed with type 2 diabetes will be excluded from the trial. However, if a HbA1C blood test level of 48mmol/mol or above is detected as a result of this study (https://cks.nice.org.uk/topics/diabetes-type-2/diagnosis/diagnosis-in-adults/), researchers will ask participant permission to contact their GP. If participant does not consent, they will be encouraged to make contact with their GP themselves. With regards to lipid profile, if a participant has a total cholesterol reading of 5mmol/L or above, triglycerides 2.3mmol/L or above, or HDL 1mmol/L or below (LDL cholesterol will be calculated from these values with a criteria of 3mmol/L or above) researchers will ask participant permission to contact their GP. If participant does not consent, they will be encouraged to make contact with their GP themselves. With regards to blood pressure, an average of 3 blood pressure measurements will be recorded at each timepoint. Researchers will ask permission to contact a participant's GP if an average blood pressure measurement of 140/90mmHg or higher is recorded Please note that an elevated blood pressure measure of concern will be immediately apparent to the researcher in terms of making contact with the participant's GP, however, HBA1C and lipid profile will not be measured until the end of the intervention due to research practicalities such as the need to analyse bloods in batches.

References

1. Threapleton DE, Greenwood DC, Evans CEL, Cleghorn CL, Nykjaer C, Woodhead C, Cade JE, Gale CP, Burley VJ. Dietary fibre intake and risk of cardiovascular disease: systematic review and meta-analysis. BMJ 2013;347:f6879 doi: 10.1136/bmj.f6879.

2. Wright JL, Sherriff JL, Dhaliwal SS, Mamo John C L. Tailored, iterative, printed dietary feedback is as effective as group education in improving dietary behaviours: results from a randomised control trial in middle-aged adults with cardiovascular risk factors. Int J Behav Nutr Phys Act 2011;8:43 [FREE Full text] [doi: 10.1186/1479-5868-8-43] [Medline: 21595978]

3. Desroches S, Lapointe A, Ratté S, Gravel K, Légaré F, Turcotte S. Interventions to enhance adherence to dietary advice for preventing and managing chronic diseases in adults. Cochrane Database Syst Rev 2013;2:CD008722. [doi:10.1002/14651858.CD008722.pub2] [Medline: 23450587]

4. McCarthy M. Higher sugar intake linked to raised risk of cardiovascular mortality, study finds. BMJ 2014;348:g1352.[Medline: 24501228]

5. Dhurandhar NV, Thomas D. The link between dietary sugar intake and cardiovascular disease mortality: an unresolved question. JAMA 2015 Mar 3;313(9):959-960. [doi: 10.1001/jama.2014.18267] [Medline: 25734737]

6. World Health Organisation (2018) Noncommunicable Diseases. Accessible via: https://www.who.int/news-room/fact-sheets/detail/noncommunicable-diseases. Accessed: 12.03.21.

7. WHO. Primary Health Care: Now More Than Ever. Geneva: World Health Organization, 2008.

8. Celis-Morales C, Livingstone KM, Marsaux CFM, *et al* (2017) Effect of personalised nutrition on health-related behaviour change: evidence from the Food4Me European randomised controlled trial. International Journal of Epidemiology, 578-588.

9. Kipnis V, Midthune D, Freedman L, *et al*. (2001) Bias in dietary-report instruments and its implications for nutritional epidemiology. *Public Health Nutr* **5**, 915-923.

10. O'Donovan CB, Walsh MC, Woolhead C, Forster H, Celis-Morales C, Fallaize R, Macready AL, Marsaux CFM, Navas-Carretero S, Rodrigo San-Cristobal S, Kolossa S, Tsirigoti L, Mvrogianni C, Lambrinou CP, Moschonis G, Godlewska M, Surwillo A, Traczyk I, Drevon CA, Daniel H, Manios Y, Martinez JA, Saris WHM, Lovegrove JA, Mathers JC, Gibney MJ, Gibney ER, Brennan L. (2017) Metabotyping for the development of tailored dietary advice solutions in a European population: The food4me study.*Br J Nutr* 118:561-569.

11. Michie S, Ashford S, Sniehotta FF, Dombrowski SU, Bishop A, French DP (2011a) A refined taxonomy of behaviour change techniques to help people change their physical activity and healthy eating behaviours: the CALO-RE taxonomy. Psychol Health 26:1479–1498. doi:10.1080/08870446.2010.540664

12. Michie S, Hyder N, Walia A, West R (2011b) Development of a taxonomy of behaviour change techniques used in individual behavioural support for smoking cessation. Addict Behav 36:315–319. doi:10.1016/j.addbeh.2010.11.016

13. Fung TT, Isanaka S, Hu FB, Willett WC. International food group-based diet quality and risk of coronary heart disease in men and women. Am J Clin Nutr. 2018;107:120-129. PMCID: PMC5972643

14. Erwin C. Development and evaluation of a pilot feasibility trial to encourage adoption and maintenance of a mediterranean diet. PhD Thesis. 2018.

15. Abubucker S, Segata N, Goll J, Schubert AM, Izard J, Cantarel BL, Rodriguez-Mueller B, Zucker J,Thiagarajan M, Henrissat B, White O, Kelley ST, Methe B, Schloss PD, Gevers D, Mitreva M, Huttenhower C. Metabolic reconstruction for metagenomic data and its application to the human microbiome. PLoS Comput Biol. 2012;8:e1002358. PMCID: 3374609

16. Segata N, Waldron L, Ballarini A, Narasimhan V, Jousson O, Huttenhower C. Metagenomic microbial community profiling using unique clade-specific marker genes. Nat Methods. 2012;9:811-814. PMCID: 3443552

17. Morgan XC, Tickle TL, Sokol H, Gevers D, Devaney KL, Ward DV, Reyes JA, Shah SA, LeLeiko N,Snapper SB, Bousvaros A, Korzenik J, Sands BE, Xavier RJ, Huttenhower C. Dysfunction of the intestinal microbiome in inflammatory bowel disease and treatment. Genome Biol. 2012;13:R79. PMCID: 3506950

18. Chiuve SE, Fung TT, Rimm EB, Hu FB, McCullough ML, Wang M, Stampfer MJ, Willett WC. Alternative dietary indices both strongly predict risk of chronic disease. J Nutr. 2012;142:1009-1018. PMCID:3738221

19. Fung TT, Chiuve SE, McCullough ML, Rexrode KM, Logroscino G, Hu FB. Adherence to a dash-style diet and risk of coronary heart disease and stroke in women. Arch Intern Med.

20. Fung TT, Rexrode KM, Mantzoros CS, Manson JE, Willett WC, Hu FB. Mediterranean diet and incidence of and mortality from coronary heart disease and stroke in women. Circulation. 2009;119:1093-1100. PMCID: 27244712008;168:713-720.

21. de Koning L, Chiuve SE, Fung TT, Willett WC, Rimm EB, Hu FB. Diet-quality scores and the risk of type 2 diabetes in men. Diabetes Care. 2011;34:1150-1156. PMCID: 3114491

22. Skivington K, Matthews L, Simpson SA, Craig P, Blazeby J, Boyd KA, Craig N, French DP, McIntosh E, Petticrew M, Rycroft-Malone J, White M, Moore. BMJ. 2021;374:n2061

23. Holtrop JS, Estabrooks P, Gaglio B, Harden SM, Kessler RS, King DK, Kwan BM, Ory MG, Rabin BA, Shelton RC, Glasgow RE. Journal of Clinical and Translational Science. 2021, 5: e126, 1-10, doi doi: 10.1017/cts.2021.789).

Figure 1: Summary flow chart of study visits