Trial Protocol

Randomised controlled fidelity trial examining the effects of high fibre breakfast cereal on plasma alkyl-resorcinol in 9-10 year old South Asian and white European children

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1. SUMMARY

Background: Type 2 diabetes (T2D) is a major public health problem both in the UK and globally; in the UK ~5% of all adults are affected. An important feature of the T2D epidemic has been the early development of T2D risk and its precursor insulin resistance in young people. In the UK, T2D risks are particularly high in specific ethnic minority groups. UK South Asians in particular have more than a sixfold higher T2D risk in adult life; these high risks in UK South Asians develop early and are apparent as high insulin resistance and hyperglycaemia in childhood. Diet and nutritional factors are strongly implicated in the aetiology of T2D in adults, but the scope of dietary and nutritional interventions to prevent T2D is currently limited, especially in childhood. Studies both in adults and in children suggest that consuming a high fibre breakfast cereal is associated with lower risks of T2D, insulin resistance and hyperglycaemia. This is consistent with the evidence from large-scale prospective studies in adults suggesting that cereal fibre rather than other fibre types is protective against T2D risk. There is a strong scientific case for establishing whether increased cereal fibre intake can reduce insulin resistance and hyperglycaemia in children, especially in UK South Asian children, given their high emerging T2D risk. However, before a large scale randomised controlled trial can address this issue, smaller scale investigations are required to assess the acceptability, feasibility and fidelity of such an intervention in children. Fidelity will be assessed primarily by examining changes in a biomarker of fibre intake, plasma alkyl-resorcinol.

Design: Primary school based study; intervention fidelity will be examined in a parallel group randomized controlled trial of one month duration.

Participants: Participants will be primary school children aged 9-10 years of South Asian and white European origin, the fidelity trial will include 400 children.

Assessments: In the initial stage of the research, children will asked about their current breakfast consumption pattern. They will be asked to report on the palatability and acceptability of a range of high-fibre cereals (each containing at least 3 grams fibre per portion) and low fibre (containing less than 1 gram of fibre) cereals. Children who report to currently eat a low fibre breakfast cereal (≤ 1 gram of fibre) and found at least one of the high fibre breakfast cereals palatable in the initial tests, will be invited to participate in a further trial to assess the fidelity of the intervention. Participants will be assessed at baseline and at the end of the one month intervention period. Assessments will include basic body composition measurements (height, weight, waist circumference, bioelectrical impedance) and a fasting blood sample for measurement of plasma alkylresorcinol. They will also be asked to complete a detailed 24 hour dietary recall and a brief food frequency questionnaire (FFQ) with a research assistant. At the end of the intervention period, both participating children and parents will be asked about the acceptability of the intervention.

Intervention (fidelity study): Intervention group participants (200 children) will be given a one month free supply of a high fibre (>3 grams fibre per portion) breakfast cereal with support and encouragement to consume this daily. Control group participants (200 children) will be given a one month supply of a low fibre (<1 gram per portion) breakfast cereal with support and encouragement to consume this daily.

Main outcome measures:

The main outcome will be the change in cereal fibre intake, assessed using a biomarker (plasma alkyl-resorcinol) and by dietary assessment (24 hour recall and FFQ).

2. BACKGROUND AND RATIONALE

Importance of type 2 diabetes in the UK:
Within the UK, 2.5 million adults have diabetes, 7.0% of men and 4.9% of women; 90% of these have type 2 diabetes (T2D) ([1]). Both incidence and prevalence of T2D are increasing markedly; it has been predicted that by 2025, 5 million adults in the UK will have T2D ([1]). The condition is associated with high cardiovascular risks and a wide range of micro-vascular complications. It is also very expensive, costing £10 billion a year (~10% of the NHS budget). There is a substantial burden of undiagnosed T2D (in at least 2% of both men and women) ([2]). A striking feature of the current UK T2D epidemic has been the declining age of onset of the condition in children and adolescents ([3]), reflecting a marked increase in T2D incidence among young people ([4]). Efforts to prevent T2D are urgently needed.

Importance of type 2 diabetes in UK South Asians:
Type 2 diabetes risks are high in specific UK ethnic minority groups, particularly UK South Asians. Compared with white Europeans, age-adjusted prevalence are 4-6-fold higher in UK South Asians ([5,6]); comparable differences in T2D incidence have also been reported ([7]). The higher T2D risks in South Asians are associated with higher population-wide levels of insulin resistance and hyperglycaemia in adults ([5,8]). These higher risks emerge early in life. UK South Asians have markedly higher T2D risks than white Europeans at <17 years ([4]). These differences in T2D risk are also reflected by population-wide differences in T2D precursors in childhood. In a recent study of T2D precursors in ~5000 9-10 year-olds, we showed that UK South Asian children had markedly higher fasting insulin and HOMA insulin resistance than white Europeans (by 30-50%); they also had higher glycated haemoglobin (HbA1c) and triglyceride levels([9,10]). These findings suggest that the determinants of higher T2D risks in South Asians are operating in childhood and offer important possibilities for early T2D prevention. Such early prevention may be important in minimizing pancreatic beta-cell damage ([11]). Diet and nutrition are potentially important determinants of T2D in this context, offering important scope for T2D prevention.

Importance of diet and nutrition in type 2 diabetes risk:
Diet, eating patterns and nutrition are strongly implicated in the causation of T2D in adults ([12,13]). Although the key components of diet and nutrition remain uncertain, diets which are low in dietary fibre are strongly associated with increased T2D risk ([14,15]). Among eating patterns, the omission of breakfast may be particularly important, being associated with increased T2D prevalence ([16]) and insulin resistance([17]); this may reflect the importance of cereal and fibre consumption ([18]). These factors could be particularly relevant in UK South Asians, who have a low fibre diet (particularly among Bangladeshis) ([19]). Although the impact of intensive overall dietary advice in people at high risk of type 2 diabetes has been encouraging ([20]), few trials have examined the effect of specific dietary or nutritional interventions on T2D risk. The influence of diet and nutrition on emerging risks of T2D in young people (particularly on the development of insulin resistance, an important precursor of diabetes) is limited; published studies have generally been small and lacked statistical power. I am currently investigating the dietary determinants of insulin resistance and other T2D precursors in ~2000 children of predominantly South Asian and white European origin, in whom I have previously reported ethnic differences in diet ([19]). The results are substantially consistent with earlier observational findings in adults in showing that children who do not eat breakfast or have a low fibre breakfast have higher insulin resistance and glycaemia ([21]). These observations could also help to explain ethnic differences in emerging T2D risk. UK South Asian children, particularly children of Bangladeshi origin have lower fibre intakes, which could help to explain their higher levels of emerging T2D risk.

Limitations of the current evidence and rationale for research:
Current evidence, both from my own research and that of other investigators, suggests that regular consumption of a high fibre breakfast is likely to reduce long-term T2D risk in children. However,

although a small number of nutritional interventions have been conducted in adults ([22]) evidence is based almost entirely on observational data and prone to confounding (particularly by socioeconomic factors and health status) and bias, and includes little or no evidence from South Asian populations. In the absence of robust evidence from randomized controlled trials, the causal implications and the scope for dietary-nutritional prevention of diabetes and its precursors, particularly insulin resistance, remain uncertain. Therefore we propose to develop a highly focussed nutritional intervention to increase breakfast fibre intake in UK children of South Asian origin, a group with high average levels of insulin resistance and long-term T2D risk. At this initial stage the feasibility, acceptability and fidelity of the intervention will be explored, the specific aim of the trial is to collect physiological outcome data on changes in biomarkers of intake only.

Statement of trial conduct
The trial will be conducted in compliance with the protocol, GCP and the relevant regulatory requirements.

3. Study aims and objectives

This study aims to develop and evaluate a specific nutritional intervention designed to increase cereal fibre intake in UK children of South Asian and white European origin. The feasibility, acceptability and fidelity of the intervention will be examined using a combination of palatability tests, questionnaires, biomarkers of cereal fibre intake (plasma alkyl-resorcinol) and dietary intake data.

Specific objectives:

1. To develop a nutritional intervention for use in UK South Asian and white European children, this will provide a breakfast meal containing at least 3.5 gram/day of cereal fibre.

2. To examine the acceptability of this intervention in children and the feasibility of providing the intervention through Primary Schools to encourage high-fibre breakfast consumption in the home setting.

3. To conduct a preparatory randomized controlled trial which will examine the fidelity of this intervention over a one month period using an objective biomarker of outcome (plasma alkyl-resorcinol).

4. Preliminary assessment

All children in the relevant classes (all year 5 classes within a participating school) will receive an invitation letter to their parent/guardian inviting them to take part in a brief survey providing information on their current pattern of breakfast cereal consumption and to test the palatability of a range of commercially available high fibre (≥3.5 gram of cereal fibre per portion) and low fibre (≤1 gram of cereal fibre) breakfast cereals. Written parental/guardian consent will be required for participation; parents/guardians will also be asked to provide key information on their child's health. Following the preliminary assessment, those children eligible (no history of diabetes, regularly consuming a breakfast cereal with fibre ≤1 gram/day, identifying a palatable high-fibre cereal in the taste test) will be invited to participate in the main trial. Parents/guardians of these children will receive a second invitation letter inviting their child to take part in the main trial. Written informed parental/guardian consent will again be required for participation. Parents/guardians of invited children will be invited to attend an induction meeting to allow parents to ask any questions they might have about the trial and also to motivate parents to support and encourage their children during the trial.

5. Study design for the fidelity trial

Description of type of trial
The trial will be a school based, parallel group randomized controlled trial with participants randomised at the individual level. The breakfast trial will compare an intervention group (high fibre breakfast cereal) with a control group (low fibre breakfast cereal) with the over a one month period.

Primary and secondary endpoints
Primary endpoint
Change in cereal fibre intake, assessed by measurement of plasma alkyl-resorcinol and dietary assessment.

Secondary outcomes (other main outcomes)
Quantitative outcomes
Changes in weight, waist circumference, fat mass index (assessed by bioelectrical impedance)
Changes in dietary nutrient intakes (24 hour dietary recall)
All changes will be based on changes between baseline and one month assessments

Qualitative outcomes: The acceptability of the intervention will be assessed using interviews and questionnaires, which will assess the views of participating children and parents on the acceptability of the interventions proposed. It will also allow the investigators to assess the acceptability and palatability of high-fibre breakfast cereals in practice.

Methods and timing for assessing, recording and analysis of outcomes: Outcome assessments (at baseline and one month) will include a dietary assessment, anthropometric measures and a fasting blood sample. These assessments will take place on the school premises during the school day. Blood samples will be taken between 08.00 and 10.30 to minimise the length of time children will be required to fast. Data will be recorded during the field survey, coding of data and data entry will be done after the field visit at St George's, Population Health Research Institute and the analysis of outcome data will occur when data on all participants is collected.

Measures taken to minimise bias
Randomisation: Randomisation will be at individual level through a computerized randomisation system.
Outcome measures: All members of the field team will be fully trained in the procedures to take measurements before the start of the field study and also familiar with the study protocol. They will be blinded to the participants' intervention status.
Statistical analysis: The data will be analysed blind to the intervention status.

6. Participant selection

School inclusion criteria: London primary schools with 40% or more of children of South Asian origin will be eligible for inclusion in the study.

Participant inclusion criteria:

Participants will be year 5 children (aged 9-10 years old), pupils at participating London primary schools. The criteria for inclusion will be as follows:-
-no history of diabetes
-currently eating a breakfast cereal with low fibre content (≤1 gram of fibre per portion)
-at least one of high-fibre cereals used in the trial found to be palatable
-written, informed parental or guardian consent provided
-able to complete trial entry assessment

Only children with parental written, informed consent will be eligible to take part in the taste test of breakfast cereals. Only children who currently eat a low fibre (≤1 gram of fibre) breakfast cereal will be eligible to be randomised to receive either a high fibre breakfast cereal or a low fibre breakfast cereal. This age group has been chosen as we have previously shown ethnic differences in fasting insulin and glycaemia by this age. An advantage is that this year group are also not involved in SATs exams. Children who regularly eat a low fibre breakfast cereal (<1 gram per portion) will specifically be invited to participate.

Recruitment of schools: School invitation letters will be sent out to a random sample of schools which meet the inclusion criteria, which will include details of the study and why we are wanting to invite the school. A reply letter with options including (a)would be willing to take part, (b) would like more information, or (c) are not willing to take part will be included. If no reply is received the PI will make follow up telephone calls to the head teachers to try and increase recruitment.
Recruitment of participants: All children in the relevant year 5 classes will be given an information sheet on the study and what participation will involve, the PI (Dr Angela Donin) will also visit each school to verbally explain the study to the children and to answer any questions which the children have about the study. Parents will be given invitation letters explaining the study and what participation will involve with a full consent form to sign. Information (age, sex, ethnicity) will be collected from the school on all children invited so non-responders can be compared to responders. Once consent has been given, participating children will be given a unique study identifier which will be used to randomly allocate them to their intervention status. At the beginning of the study the children will be made aware that they can withdraw from the study at any time, this will also be reitterated during the study period.

End of study definition: The end of the study for each participant will be after the follow-up measurements have been taken, which will be one month after the baseline measurements were taken. The end of the study overall will be when all follow-up measurements have been completed on participating children.

7. Study procedures

Informed consent procedures: Parental consent will be required for children to participate. A consent form will be included in the invitation letters which will be sent to the parents, this will give full details of the study and the measurements that will be taken. The original signed consent form will be given to the research nurse before any measurements will be taken. The children will receive study information sheets which will give details of the study and the measurements that will be taken. The PI (Dr Angela Donin) will also visit each school to talk through the study and allow children to ask any questions they may have. Before any measurements are taken each participating child will be asked if they are happy and willing to participate, they will be informed that they are free to withdraw at any point of the trial without needing to give a reason.

Assessments to be made (baseline and follow-up):

i) Fasting blood sample for measurement of cereal fibre biomarker (plasma alkyl-resorcinol)
ii) Physical measurements - height, weight, waist circumference, bioelectrical impedance
iii) Cereal fibre intake (FFQ)
iv) Dietary data – 24 hour recall

All children will be assessed at baseline by a research assistant and a research nurse. All blood samples will be taken between 0800 and 1030; children will then be given a breakfast before any other measures are taken. This will minimise the length of time children will be required to fast. The researchers who will be taking the blood samples will be trained and experienced paediatric phlebotomists. Every child will be offered an anaesthetic spray before the sample is taken. During the procedure children will also be able to watch a DVD as a distraction. Experience of taking blood samples from over 5000 children in a previous study has shown that this protocol works well and minimizes discomfort for the participant. Current diet will be assessed using a computerized 24-hour dietary recall and a 43 item food frequency questionnaire [FFQ]. Measurements of height, weight, waist circumference and bioimpedance will be made.

Procedures for control group:
After baseline measurements have been taken the children will be provided with a free one month supply of low fibre breakfast cereal with verbal and written instructions and contact details of the PI if they have any questions during the trial. An interim visit (school visit) will be scheduled after one week to encourage and support the children and resolve any issues they may have with the trial. The children will be given the date that the research team will be returning to their school to take the follow up measurements. This will be over a 2-3 day period which will minimise children being lost for follow up if they are off school for a day as the measurements may be taken on their return. Questionnaires will be given out asking the children about compliance and any behaviour change during the trial. Children will be invited to answer a brief questionnaire to assess the acceptability of the trial.

Procedure for intervention group:
After baseline measurements have been taken the children will be provided with a free one month supply of high fibre breakfast cereal with verbal and written instructions and contact details of the PI if they have any questions during the trial. An interim visit (school visit) will be scheduled after one week to encourage and support the children and resolve any issues they may have with the trial. The children will be given the date that the research team will be returning to their school to take the follow up measurements. This will be over a 2-3 day period which will minimise children being lost for follow up if they are off school for a day as the measurements may be taken on their return. Questionnaires will be given out asking the children about compliance and any behaviour change during the trial. Children will be invited to answer a brief questionnaire to assess the acceptability of the trial.

8. Safety

Risks: The trial poses a very low risk to children's health. The high fibre breakfast cereals will not include fibre intakes above daily recommended amounts and both the high and low fibre cereals are already available to purchase in shops.

Benefits: It is feasible that participants randomized to the high cereal fibre intake group will benefit from a slight reduction in their levels of insulin resistance during the fidelity trial. However, in the preliminary studies described here, no marked benefits (or harms) are expected.

9. **Statistics**

Sample size: The fidelity intervention trial will be based on 400 subjects in each of two parallel groups studied at baseline and at the end of the intervention period. This will allow reasonably precise estimates of changes in dietary fibre intake to be made. With 400 participants (200 intervention, 200 control) it will allow a mean plasma alkylresorcinol difference of 0.4 standard deviations (~14 nmol/L) to be detected with 90% statistical power at $p < 0.01$. These calculations assume a between subject SD of ~35 nmol/L for plasma alkylresorcinol. Similar standard deviation differences will apply for questionnaire-based measures of dietary cereal fibre intake. Formally, this will allow differences of less than 0.5 standard deviations in changes in fibre intake to be detected with 90% power at $p < 0.05$.

Anticipated recruitment: We anticipate a conservative recruitment rate of 50% amongst those eligible to participate. This figure is based on the higher recruitment rate of 69% achieved in a study based on the same age group and ethnicity and which also required the children to provide a blood sample. We believe that the study will be of interest both to children and parents and that the prospect of free supplies of breakfast cereal will provide an appreciable incentive. We will also offer children a gift voucher (£10 per participant) on successful completion of the study.

Statistical analysis: The principal statistical analyses will examine change in cereal fibre intake, specifically the analysis will examine the intervention-control differences in changes in dietary cereal fibre intake occurring during the intervention period. These will be examined using standard multilevel linear regression models. Additional analyses will examine the effect of adjustment for potential covariates (identified from the comparison of baseline data and a priori evidence of covariate-outcome correlation), to overcome any imbalance following randomisation. All analyses will be carried out on an Intention-To-Treat (ITT) basis.

10. **Data handling and record keeping**

Confidentiality and data protection:
All data collected will be linked using a unique study identifier which will not include personal identifier information to ensure anonymization. Data will not be directly linked to personal identifier information. St Georges, University of London has its own institutional information security and data protection policies (see http://www.sgul.ac.uk/images/about/Policies/SOP_DataProtection.pdf). Personal data are stored only on secure network drives (not removable ones). Incoming email to SGUL is scanned with 2 different virus scanners, and the mil and file servers are scanned for viruses twice daily. NOD32 desktop and server software is installed and updated every 4 hours. All access to the central SGUL servers is logged and monitored closely to prevent security violations, with an Intrusion Detection system and a quarantine system. All SGUL computers are password protected and files will also be password pretected to restrict access to those that require it. Data record forms will be either locked within the school premises or transferred to SGUL where they will be entered into password protected files on the secure SGUL network drive, and the paper copies filed in a secure archive room.

11. Ethics, compliance and clinical governance

Ethical considerations: The trial will be submitted to a relevant Reseach Ethics Committee.

Compliance: The trial will be conducted in compliance with the protocol, Good Clinical Practice and regulatory requirements.

12. Publication and dissemination policy

Results of the study will be submitted for publication in high impact open-access journals and for presentation at a range of national and international conferences; this will provide important opportunities to inform other academics and policy makers. Early information and feedback will be provided to the children and families participating in the studies. This will be done by feedback meetings held at the study schools and by the development of study newsletters providing information at an appropriate literacy level and translated as necessary. In addition, a website will be established for this research initiative, which will be regularly updated with details of the study results and associated information and advice.

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