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COMMENTARY

Cereal fibre and type 2 diabetes: time now for randomised controlled trials?

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Abstract Diet and nutrition are strongly implicated in the aetiology of type 2 diabetes; low dietary fibre intake could be an important factor. Evidence from prospective observational studies has suggested that it may be low cereal fibre intake, rather than low fruit and vegetable fibre intake, which is particularly important. In this issue of *Diabetologia* (DOI 10.1007/s00125-015-3585-9) Kuijsten et al report on the prospective associations between different dietary fibre sources and type 2 diabetes risk in the European Prospective Investigation of Cancer and Nutrition (EPIC)-Interact study and set their findings in context with a meta-analysis of relevant published prospective studies. The results presented strengthen the evidence implicating cereal fibre as an important determinant of type 2 diabetes risk and suggest that randomised controlled trials examining the effect of cereal fibre supplementation on type 2 diabetes risk are now needed.

Keywords Aetiology (Etiology) · Diet · Fibre (Fiber) · Nutrition · Prevention · Type 2 diabetes

Abbreviation

EPIC European Prospective Investigation of Cancer and Nutrition

Although diet and nutrition are widely regarded as being of fundamental importance in the aetiology of the evolving global type 2 diabetes epidemic [1], progress in defining the specific dietary determinants of type 2 diabetes risk remains far from complete. One potentially important dietary factor, low fibre intake, was highlighted by Trowell 40 years ago, in his observation in East Africa that dietary fibre intake was high and type 2 diabetes virtually unknown [2]. Subsequent experimental studies in patients with established diabetes showed that sustained dietary fibre supplementation reduced fasting glucose and HbA_{1c} levels.

Evidence on the role of high dietary fibre intake in the aetiology of type 2 diabetes had to await the results of large-scale prospective observational studies relating habitual diet and type 2 diabetes risk in adult populations. From the start, these results suggested not only that higher total dietary fibre intake was associated with lower type 2 diabetes risk, but also that cereal fibre might be particularly important [3]. In 2007, Schulze and colleagues combined the presentation of novel data from the European Prospective Investigation into Cancer and Nutrition (EPIC) Potsdam cohort with an overview of the available prospective evidence relating fibre of cereal, fruit and vegetable origin with type 2 diabetes risk, including data from eight other cohort studies [4]. The results of their meta-analyses (based on more than 300,000 participants and 8,500 type 2 diabetes cases, from predominantly US populations, and adjusted for 'lifestyle' factors and BMI), showed an inverse graded association between cereal fibre intake and type 2 diabetes risk; the highest cereal fibre intake groups (mainly top fifths) had a relative risk (RR) of 0.67 (95% CI 0.62, 0.72) for type 2 diabetes risk when compared with the lowest fifth of cereal fibre intake. In contrast, neither a high intake of fruit fibre (RR 0.96), nor a high intake of vegetable fibre (RR 1.04), were appreciably associated with type 2 diabetes risk; these estimates had sufficient precision to exclude RR reductions of ~15% with a high degree of confidence. The case for the importance of cereal fibre was strengthened by separate observations that regular breakfast

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consumption, particularly of whole grain cereal, was associated with lower type 2 diabetes risk [5].

In the current issue of *Diabetologia*, Kuijsten et al [6] report further large-scale evidence on the prospective associations between different subtypes of dietary fibre intake and type 2 diabetes risk. Their analyses are based on the EPIC-Interact case-cohort study, carried out in 11,559 type 2 diabetes cases and 15,258 randomly selected participants, drawn from EPIC cohorts in eight European countries. Again, the results are helpfully set in context with updated meta-analyses of relevant published prospective studies relating fibre intakes from different sources to type 2 diabetes risk. The results presented in this new report further strengthen evidence for the primacy of high cereal fibre intake over other forms of fibre as a determinant of lower type 2 diabetes risk. In the EPIC-Interact study, the highest quartile of cereal fibre intake was associated with a lower risk of type 2 diabetes (HR 0.81, 95% CI 0.70, 0.93) compared with the lowest quartiles (a difference of about 9 g/day of cereal fibre) even after adjustment for 'lifestyle' factors (particularly cigarette smoking and physical activity) and other components of diet. EPIC-Interact analyses of other dietary fibre types suggested that high vegetable fibre intake was also associated with a lower risk of type 2 diabetes (HR 0.84, 95% CI 0.74, 0.96), though fruit fibre showed no clear association with type 2 diabetes risk. The associations for cereal and vegetable fibre were, however, attenuated by adjustment for BMI. The new meta-analyses presented by Kuijsten et al examining the associations between specific fibre intakes and type 2 diabetes risk [6] add appreciably to those presented by Schulze et al [4], with almost a twofold increase in participants and more than a fourfold increase in type 2 diabetes cases, in a more diverse range of populations. The results of these new meta-analyses suggested that a 10 g higher daily cereal fibre intake was associated with an appreciably lower RR of type 2 diabetes, in analyses that adjusted for both dietary and non-dietary confounders and for BMI (RR 0.75, 95% CI 0.65, 0.86). However (and in contrast with the EPIC-Interact findings for vegetable fibre, although in agreement with the earlier meta-analyses by Schulze et al [4]) the new meta-analyses showed no association between either fruit or vegetable fibre and type 2 diabetes risk. The association between cereal fibre and type 2 diabetes risk appeared to be graded (though increasingly steep at higher cereal fibre intakes) and similar in strength for both soluble and insoluble fibre, although no formal analysis of different cereal fibre sources (e.g. wheat and oat-based) was presented. The findings are consistent with those of another recent review of the evidence linking fibre intake and type 2 diabetes [7].

The new study and associated meta-analyses reported by Kuijsten et al [6] have several important strengths (including prospective design, large size, wide exposure range and detailed assessment of a wide range of potential confounders, both dietary and non-dietary). The major limitation (as the authors recognise) is the imprecision in assessment of dietary intake at baseline, based on semi-quantitative food frequency questionnaires both in the EPIC-Interact study and in most of the other prospective studies in the meta-analysis, and the absence of information on changes in dietary intake during follow-up. However, these sources of error are likely to have led to underestimation, rather than overestimation, of the true strength of association between cereal fibre intake and type 2 diabetes risk. Underestimation is also likely because the associations were adjusted for BMI (potentially a mediator of the cereal fibre–type 2 diabetes association, given the well-established association between body fatness and type 2 diabetes risk). Taking the evidence as a whole, the inverse association between cereal fibre intake and type 2 diabetes risk has been consistent in large prospective population-based studies, appears graded and is substantially independent of measured confounding factors. The association is also biologically plausible, with several potential mechanisms implicated. The results of EPIC-Interact raised the possibility that high cereal fibre intake might act at least partly by reducing body fatness, consistent with earlier reports relating high cereal fibre intake to lower body fatness [8]. However, the results of both the current meta-analyses reported by Kuijsten et al [6] and the earlier meta-analyses of Schulze et al [4] suggest that the cereal fibre–type 2 diabetes association is substantially independent of body fatness as measured by BMI, for which adjustment was made in almost all studies included in these meta-analyses. This suggests that a range of other previously reported mechanisms, including the effects of soluble cereal fibre components in inhibiting macronutrient absorption and reducing postprandial glucose response, and the effects of the insoluble fibre component on insulin sensitivity [9], could be of greater importance.

Taken together, the evidence makes a persuasive case for potential causality, to which further observational studies are unlikely to add appreciably. To advance our understanding, the most important priority now is to carry out well-designed randomised controlled trials examining the influence of cereal fibre supplementation on type 2 diabetes risk [10]. Evidence from such trials would have an important impact on the debate about causality; if positive, such evidence would help to underpin public health nutritional strategies for type 2 diabetes prevention.

The auguries for such trials are favourable. The Finnish Diabetes Prevention Study included advice to increase fibre intake as one of its components; participants with higher fibre intake had a reduced type 2 diabetes incidence [11]. Experimental studies have shown that short-term increases in cereal fibre intake reduce insulin resistance in adults [12]. A key priority is for explanatory trials examining the effect of cereal fibre supplementation in adults at exceptionally high risk of type 2 diabetes, logically following the model of earlier type 2 diabetes prevention trials in high-risk population

groups [13]. In addition, further short-term intervention studies examining the effects of cereal fibre supplementation on insulin resistance and glycaemia could be informative both in adults and in children, particularly in the light of recent evidence that higher cereal fibre intake is associated with lower insulin resistance in childhood [14]. In the meantime, the existing evidence fits within a broader public health case for increasing overall dietary fibre intake to reduce the incidence of a wide range of chronic diseases including cardiovascular disease and colorectal cancer [7, 10], while emphasising the particular importance of increasing cereal fibre intake for type 2 diabetes prevention. Increasing the fibre content of breakfast cereals, which are widely consumed in many parts of the world, could prove an important mechanism both for the translation of trial findings and for reducing risks of type 2 diabetes and other chronic diseases worldwide.

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