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Invited Commentary

Quantile regression reaches the parts that mean regression may not: insoluble dietary fibre and glycaemic index in type 2 diabetes

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We are accustomed to summarising many results from nutritional studies on groups of people as the mean or mean trend from regression analysis, and informing about the dispersion of results with the standard deviation among observations from participants, which may be minimally or largely due to experimental error. However, what if the dispersion is largely due to real differences (heterogeneity) among study participants? Quantile regression (QR) can provide an answer and be highly informative.

In this issue of the *British Journal of Nutrition*, Tan *et al.*[1] use QR to provide observations from a small prospective cohort study that supports at least six findings of potential importance for the development of medical nutrition therapy for diabetic patients[1]. These findings are: (1) That the 5-year change in the blood concentration of a marker for glycaemic control in type 2 diabetes (T2D)[2], namely non-enzymatically glycosylated (i.e. glycated) Hb (HbA_{1c}), associates with dietary fibre intake. (2) That this association occurs with insoluble dietary fibre, whereas certain soluble fibres have long been considered favourable for improving glycaemic control and is still being researched[3,4]. (3) That the association for T2D is not only evident in Western ethnicities, but also among the Chinese population as shown by meta-analyses[5,6] (and in type 1 diabetic patients in Europe[7]). (4) That among Chinese T2D patients, the association is stronger in those with higher concentrations of HbA_{1c} (poorer glycaemic control), as is the case in Western T2D patients for markers such as glycated proteins, fructosamine and fasting blood glucose as shown by meta-regression analyses[6]. (5) That a similarly important association exists between the change in HbA_{1c} values and the glycaemic index (GI) of ingested carbohydrate among Chinese T2D patients, as is found also in Western T2D patients for glycated proteins, fructosamine and fasting blood glucose as shown by meta-regression analyses[6] (and in European type 1 diabetic patients[8]). Finally, (6) that these findings within a prospective cohort study can be reached by the currently less-known estimation procedure of QR, but they might not be reached either by commonly used means regression (MR)[9] or meta-regression (meta-MR) when combining studies unless attention is given to appropriate modelling of predictor variables[6,10,11].

Even with QR, care must still be taken. Results analysed by QR are still subject to some weaknesses arising from study methodology. Those from Tan *et al.*[1] are weakened, in part, by the small study size, which is likely to make the differences between reported associations by QR unclear. Clarity is likely to be weaker still because food intakes in their study were assessed using a FFQ with a marginal instrumental validity (instrument's correlation with an accurate assessment method) of only 0·53 for insoluble dietary fibre. Meanwhile, correlations for the GI and carbohydrate were not reported. Notably, poor correlations will lead to marked underestimation of associations in prospective cohort studies and may even result in the failure of finding any association[11–13]. For many a reader, clarity is likely to appear weaker still because QR is currently not a familiar statistical procedure. Hence, considering these weaknesses together, Tan *et al.*'s study[1] inevitably informs us about the uncertain strengths of the association (probably underestimates) between the change in HbA_{1c} concentrations over 5 years and insoluble dietary fibre and GI intakes at each possible quantile of HbA_{1c} (their[1] Table 2 and Figs. 1 and 2).

Nevertheless, QR has several advantages over MR. QR is less influenced by outliers, makes no assumption about the equality of variances across the range of values for predictor variables, and can inform about the shape of the association across the values of predictor variables, i.e. no assumptions are made about a relationship being either linear or curvilinear in any pre-specified form; meanwhile, intercepts and slopes are not assumed constant from one quantile to another. Interestingly, the observations from Tan *et al.*[1] indicate a possible broadly inverted U-shaped relationship for the size of associations for the decrease in HbA_{1c} concentrations with higher insoluble fibre intake (their Fig. 1) and a possible broad U-shaped association between the increase in HbA_{1c} concentrations and higher GI in the upper quantiles (their Fig. 2). While these shapes remain to be confirmed in further studies, MR either alone[9,14] or without appropriately specified covariates (as has been used in meta-analyses[6,10,11]) may not have found any association or effect. Having a larger dataset and using an FFQ with high instrumental correlations would be expected to result in greater accuracy and precision, and enable tests of significance for the difference in the size of

associations at different quantiles[15]. Furthermore, as in MR, multiple predictors can be used in QR simultaneously; however, advantageously QR reports on the size of associations across all possible quantiles for predictor variables rather than reporting on the mean intercept or the mean trend as obtained from MR[15].

Some differences exist in the observations made between their Chinese patients with T2D (5-year follow-up in prospective cohorts, which are non-randomised)[1] and counterparts of Western ethnicities in whom fibre and GI acted independently (<6-month follow-up in randomised controlled trials)[6], but their findings are similar. Moreover, results of these publications are consistent with other studies (6-year follow-up in prospective cohorts) showing that both cereal fibre and GI via glycaemic load (GL), independently of one another, associate with the incidence of T2D[16,17]. Furthermore, regular intake amounts of monosaccharide fructose (low GI) replacing glucose or starch, independently of fibre, lowers the levels of HbA_{1c} in Western patients with T2D[10]. The relationship between GL and T2D is now reported as stable in a systematic review using cumulative meta-regression analysis and pre-published hypotheses on all twenty-five prospective cohort studies available in the literature, and reported significantly for both women and men and for different ethnicities, with 97% of heterogeneity among studies reviewed having been explained[11,18].

Other similarities exist among the various studies. Tan *et al.*'s observations[1] show the strongest association between HbA_{1c} and GI occurs among T2D patients having the poorest control of blood glucose levels as marked by their HbA_{1c} concentration. Similar findings for dietary GI and GL arise from a meta-regression analysis of intervention studies concerned mainly with starchy foods[6], or with the monosaccharide fructose replacing glucose or starch, so lowering the GI of diets[10]. Similar findings were also obtained for the effect of drugs on glycaemic control in patients with T2D.

It is increasingly evident from comparisons among interventional studies[6,10], among prospective cohort studies[11], and within the prospective cohort study of Tan *et al.*[1] that human nutrition studies are more complex than catered for by the regularly used MR and meta-analysis without appropriate modelling (which may include quotients or products of predictor variables). Generalising from these observations, no two studies examining the same issue from within or among laboratories can be assumed alike, and no two participants examined within a study can be assumed alike even when categorised similarly for clinical purposes. Such heterogeneity within and among studies is common, and failure to account for it can lead to results with an imprecise estimate of effects or associations, and failure to find truer probabilities or even any effect or association at all, as colleagues of Tan *et al.* report in an earlier publication[9].

Complexity in nutrition is evident, a situation for which QR is applicable, and possibly no less so in human nutrition than in micro-econometrics[15] or ecology or other biological studies[14]. Students may find that the use of QR makes for an interesting chapter in their thesis, and a learning experience with little need for additional data if already using MR on moderate to large datasets. Health professionals and researchers may find QR useful because it provides results more closely applicable to individuals or individual circumstances than does MR.

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