Can we out-run the diabetes epidemic?

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According to the WHO, the worldwide prevalence of diabetes in 2030 is expected have doubled from the year 2000 estimate of 171 million [1]; by all estimates, the prevalence of type 2 diabetes has already reached epidemic proportions in the developed world. Observational studies have demonstrated that, with few exceptions, overweight and obesity are almost ubiquitous in type 2 diabetes, and the relatively large projected growth in the prevalence of diabetes in the developing world is largely attributable to the spread of overweight and obesity. Intervention programmes to prevent the development of diabetes should therefore focus on reversing overweight and obesity, which underlie this devastating disease.

When the findings from the Diabetes Prevention Program (DPP) were first announced in 2002 [2], the scientific community was not surprised to learn that study participants in the intensive lifestyle intervention arm had a lower risk of developing diabetes than their counterparts in the placebo arm. The surprising finding was that intensive lifestyle intervention, based on dietary energy restriction and encouragement to engage in moderate physical activity on most days of the week, with a goal of achieving 7% weight loss [3], performed better than metformin in preventing high-risk participants from developing diabetes. Later evidence that the intensive lifestyle intervention was a cost-effective alternative to pharmacological therapy [4] re-emphasised the benefits of diet and exercise in the prevention of diabetes.

If lifestyle intervention is such a resounding success, why is it important to determine whether it is diet or physical activity that is driving the success? The answer to that question lies in the difficulty individuals have in adopting lifestyle changes. Compliance with lifestyle intervention certainly varies between individuals, but inter-individual variability in the physiological responses to diet and exercise is even greater. By simplifying interventions to focus on the most effective component, or the component that is easiest to adopt (as the two are not often the same), we might improve compliance with the intervention and thus achieve greater success in preventing disease.

In this issue of *Diabetologia*, Yates et al. [5] report on a systematic review of clinical trials to determine whether the physical activity component of lifestyle interventions prevents the development of diabetes or lowers fasting or 2-h blood glucose levels in participants with impaired fasting glucose or impaired glucose tolerance. The stated goal of the review is to determine whether physical activity demonstrates a protective association with incident diabetes, independently of dietary energy restriction. The authors summarise the findings from eight controlled trials and report that lifestyle interventions reduced the incidence of diabetes by approximately 50%, but that there was little decrease in blood glucose during the intervention period. None of the studies could determine whether the reduction in risk was independent of weight loss. Based on these results, Yates and colleagues conclude that the evidence for exercise interventions in preventing the development of diabetes is equivocal. Further, the authors advance the hypothesis that the reduction in diabetes incidence is probably attributable to factors other than increased physical activity since, when measured, actual changes in physical activity were minimal.

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The final conclusion by Yates and colleagues is disappointing, given observational evidence that higher levels of physical activity and fitness lower the risk of developing diabetes [6–10]. However, the story is not complete. Their conclusion appears to be driven by the lack of association between physical activity and continuously-measured 2-h glucose, which was the outcome in some, but not all, of the studies included in the review. Yates' enthusiasm for the inverse association observed between physical activity change and the development of clinical diabetes is mitigated by the minor changes in 2-h glucose measurements. I do not believe that the findings from these particular studies warrant a conclusion of "no effect", since Yates and colleagues acknowledge that the measurement of 2-h plasma glucose has poor repeatability, which could have obscured the changes. Additionally, I would argue that the goal of any intervention trial in high-risk participants is to delay the development of disease. If we adhere to this principle, then a flat slope for the change in 2-h plasma glucose over time represents a success—glucose levels are not creeping up to the cut-off point that defines clinical diabetes in those individuals exposed to the physical activity intervention. The authors correctly stated their inability to isolate the protective effects of increased physical activity compared with dietary energy restriction. Consequently, this important question remains unanswered, because the trials that were reviewed asked a different question than that posed by Yates et al. in their review.

In an effort to describe the types of evidence we need, I will reiterate why it is important to understand the role of physical activity in preventing the development of diabetes in high-risk persons. Individuals respond to and adhere to different components of a multi-part intervention based on their readiness to change, sense of self-efficacy to make a change, and ability to overcome real and perceived barriers to change. The same individual who feels unprepared to change their diet may eagerly respond to the opportunity to participate in a dance class or daily walking group as part of an intervention. Similarly, if the target of an intervention is weight loss, and study participants are monitored regularly for progress towards the goal, a study participant who is not losing weight may become frustrated and give up trying to adhere to the intervention. If, however, we learn that the real protection against diabetes comes from improved cardio-respiratory fitness or from better micro- or macro-nutrient composition of the diet—independent of weight loss—then a participant has "failed" to prevent diabetes by giving up prematurely.

Investigators who are studying dietary change and physical activity compliance have traditionally had to rely on a study of participant's self-reported adherence to the intervention once that individual leaves the research

laboratory. Physical activity measurement, however, has the benefit of available non-invasive objective measures that can be used to determine adherence and response. Accelerometers can be used to assess compliance with activity prescriptions; pre- and post-exercise testing to determine maximal oxygen consumption can be measured in the laboratory to evaluate changes in cardio-respiratory fitness—the physiological response to physical activity. The ready availability of both objective testing modalities makes it feasible to design an intervention study in high-risk individuals that not only recommends physical activity levels but determines adherence to that exercise programme and the physiological response to that programme.

Even without the introduction of such technology, a study design similar to that of the Diet Exercise and End Results (DEER) trial that separately evaluated the role of dietary energy restriction, exercise, and the combination of diet and exercise on lipid-lowering, could be conducted, with the outcome being the development of diabetes [11]. Based on what we know about the joint benefits of diet and exercise, our *a priori* hypothesis might be that (as occurred in the DEER trial) the combination of diet and exercise would produce the greatest weight loss and thus provide the greatest protection against the development of diabetes. Alternatively, the "fit vs fat" hypothesis, that overweight individuals who are in good cardio-respiratory fitness experience mortality rates that are better than their lean but unfit peers [12], provides a backdrop to test the hypothesis that physical activity that results in improved fitness provides protection against the development of diabetes.

We should also design studies to evaluate the type, frequency and intensity of physical activity required to provide protective benefits. Overweight or obese individuals are more likely to suffer from arthritis and other debilitating musculoskeletal injuries that preclude the adoption of a vigorous exercise programme. Many others have metabolic syndrome comorbidities, including dyslipidemia and high blood pressure, that warrant physician-monitoring of high-intensity activities. Thus, an equally important goal should be investigating whether light- to moderate-intensity physical activities provide any health benefits. There is evidence for insulin-sensitising effects of resistance training [13]; whether these sensitising effects delay the development of clinical diabetes among those who are already high risk is not known. Even lower-intensity activities that focus on posture, breathing and flexibility, such as yoga, Pilates or T'ai Chi, may be culturally appropriate in some subpopulations and are almost universally palatable for older adults. It is not known whether these activities provide any benefits beyond that of increasing one's readiness for more moderate or vigorous physical activities.

Currently, the American Diabetes Association [14] recommends physical activity as an essential component to maintain weight and lower one's risk of developing diabetes. Evidence for these recommendations comes from many of the studies reviewed by Yates and colleagues, as well as the handful of observational studies showing an inverse association between physical activity and the development of diabetes. However, as highlighted in this issue of the *Diabetologia*, the evidence for a beneficial effect of physical activity alone does not exist. Now that the science has identified physical activity as a plausible preventive measure, additional well-designed studies are needed to determine: (1) the contributions of exercise independent of dietary restriction; (2) the type, frequency and intensity of physical activity required to prevent diabetes; and (3) whether activity independent of weight loss provides any benefit. It is only when we can answer these questions that we can hope to look over our shoulders and out-run the rapidly approaching worldwide diabetes epidemic.

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