Screening for type 2 diabetes: Does the ADDITION–Cambridge trial distract from the real policy challenge?

Diabetes mellitus (DM) is a major, growing and costly public health problem. It affects 371 million people worldwide, 80% of whom live in low- and middle-income countries (LMICs).1 About 90%–95% of people with DM worldwide are type 2 (T2DM), which is the major contributor to the rising burden of diabetes.2 The epidemic is no longer limited to urban and affluent societies but is rampant even in rural parts of LMICs.3 Diabetes causes 4.8 million deaths each year. The disease is prolific in its complications, which include cardiovascular, eye and kidney diseases, amputations and a higher risk of infections.4,5 Yet, even in a high-income country such as the USA, about 30% of people with T2DM remain undiagnosed. This proportion is as high as 50%–80% in LMICs, which are now at the epicentre of the epidemic.6 In this context, screening for diabetes is a topic of great interest, and reviews have carefully weighed its pros and cons.7 However, consensus remains elusive due to a lack of direct data from randomized controlled trials on the benefits and costs of screening.

The ADDITION–Cambridge trial was designed to fill this gap and provide information about screening for T2DM by directly comparing participants randomly assigned to screening versus no screening on mortality outcomes.8 The trial was a primary care-based, two-phase, cluster-randomized intervention study done in the context of a high-income country, with good primary care infrastructure and a T2DM prevalence of about 3% at baseline. The first phase of the trial was a parallel design, comparison of outcomes in persons screened for diabetes with persons not screened, and the second phase was a comparison of multifactorial intensive therapy with regular care in those screened. Simmons et al. recently reported the results of the first phase of the study which screened primary care clinic populations for T2DM.9

Briefly, 138 general practices in eastern England were invited by letter to participate. Of these, 63 consented to participate, of whom 30 were excluded (3 were used for piloting the trial and 27 were used in the second phase of the study). The remaining 33 clinics were stratified based on the number of people with diabetes in the practice (<160 and ≥160) and randomized in a 1:3:3 ratio by the method of minimization to the three arms of the study—no screening (n=5), screening followed by multifactorial intensive therapy (n=15) and screening followed by regular care (n=13). The latter two groups were the screening arm of the study. Of all attending patients, 16 047 subjects aged 40–69 years were identified for further step-wise screening tests using a previously validated risk score based on age, gender, body mass index and medication data from electronic health records.10 The step-wise screening included random capillary blood glucose and glycated haemoglobin (HbA1c), followed by a fasting capillary blood glucose test and a confirmatory 75 g post-load oral glucose tolerance test. No screening was offered to 4137 subjects attending the five practices in the control group. The primary outcome of all-cause mortality and secondary outcomes of death from cardiovascular disease, cancers, other causes and diabetes-related death were ascertained from national mortality surveillance data over a period of 9.6 years.

The comparison of screening and control groups was done using a Cox proportional hazards model. Since randomization was at the practice level, standard errors were
calculated taking into account the two-level structure of the data. The screening arm \(n=16\,047\) in 27 clusters and control arm \(n=4137\) in 5 clusters were comparable on most variables, other than a higher general practitioner time equivalent and a lower deprivation score in the control group. In the practices that were screened, only 466 persons (3%) had previously undiagnosed diabetes. During a median follow-up of 9.6 years, all-cause mortality did not differ significantly between the screening and control groups (HR 1.06, 95% CI 0.90–1.25, \(p=0.46\)) and neither did cardiovascular mortality, cancer mortality or other causes of death. Compared with attenders, non-attenders for screening were younger, more obese, more likely to be men, less likely to be taking antihypertensive drugs and had twice the risk of all-cause mortality (adjusted HR 2.01, 95% CI 1.74–2.32).

The results of the ADDITION–Cambridge trial thus indicate that in a population with a baseline T2DM prevalence of 3%, one-time screening does not impact mortality over 9.6 years of follow-up. It would be wrong to interpret these results literally for policy, as several contextual factors need to be thoughtfully considered. Most importantly, the trial was conducted in a high-income country population with good primary care infrastructure and found only 3% with undiagnosed diabetes. This is in stark contrast to many other countries where the prevalence of undiagnosed DM is several-fold higher.\(^1\) Furthermore, as only 33 clusters were available for randomization, the power of the trial was clearly limited. Also, the outcome was limited to mortality, but T2DM imposes considerable morbidity and substantial personal, healthcare and economic burdens. There is robust evidence that control of glucose, blood pressure and lipids can reduce mortality and cardiovascular, renal and eye complications in people with T2DM.\(^{11,12}\)

From a larger policy perspective, the early detection and treatment of prediabetes (i.e. impaired glucose tolerance and/or impaired fasting glucose) and diabetes are inseparable, in that they are part of the same continuum with an annual risk of progression from prediabetes to diabetes of 5%–10%,\(^{13}\) are detected by the same tests, and benefit from the same initial treatment (i.e. lifestyle intervention and/or metformin).\(^{14,15}\) More importantly, there is strong evidence from randomized trials that among people with prediabetes, lifestyle modification substantially reduces the incidence of diabetes, a benefit that persists for more than 20 years and may also impact reduction in microvascular complications and mortality.\(^{16–20}\) The number of adults with prediabetes worldwide is projected to reach 430 million by 2030\(^{21}\) and even in a high-income country such as the USA, 93% of people with prediabetes remain undetected.\(^{22}\)

In order to translate the evidence for prevention of diabetes into policy and practice, we need strategies to detect people with prediabetes and facilitate effective lifestyle interventions. Such screening for prediabetes will inevitably also detect people with undiagnosed diabetes, and some data suggest that a combined screening for diabetes and prediabetes may be a cost-effective strategy.\(^{23}\) Furthermore, early initiation of lifestyle treatment for people with diabetes may also increase the probability of remission to normoglycaemia.\(^{15}\) In the Look Ahead trial, as many as 11.5% of participants of the lifestyle intervention group had partial or complete remission within the first year of intervention and 7% had partial or complete remission after 4 years. These rates were three to six times those of participants in the control group.

Therefore, contrary to the message that the ADDITION–Cambridge trial may suggest, screening for DM could well be an important and effective policy tool, especially in populations with a high prevalence of diabetes and a high proportion of people with undiagnosed diabetes, which is the situation in most LMICs. Furthermore, LMICs also seem to have a high frequency of diabetes at much younger ages than the mean age of 58 years in the ADDITION–Cambridge trial, and data suggest that screening may be more cost-effective in higher-risk and younger populations.\(^{24}\)

A screening policy for diabetes and prediabetes may also stimulate opportunities to address other cardiovascular risk factors in an integrated manner, as a high proportion of people with prediabetes and diabetes have multiple cardiovascular disease risk factors.\(^2\) Therefore, a context-based policy for diabetes screening may help propel healthcare toward an innovative preventive orientation for non-communicable diseases (NCDs), with an emphasis on delivery of effective lifestyle intervention. However, for the potential benefits of screening for diabetes to be realized, it should not be conducted as an isolated or ad hoc action, but instead be made part of an organized health system that has in place mechanisms for screening, follow-up and appropriate delivery of high quality interventions in a consistent manner.
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