

Should we screen for type 2 diabetes among asymptomatic individuals? Yes

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Abstract RCTs of whether screening asymptomatic individuals for undiagnosed diabetes results in reduced mortality or has other benefits have been suggestive, but inconclusive. In this issue of *Diabetologia*, two additional controlled studies (DOIs: [10.1007/s00125-017-4323-2](https://doi.org/10.1007/s00125-017-4323-2) and [10.1007/s00125-017-4299-y](https://doi.org/10.1007/s00125-017-4299-y)) that investigated whether screening for type 2 diabetes in asymptomatic individuals is associated with a reduction in mortality are presented. Treating diabetes early, and identifying and treating impaired glucose tolerance, are of benefit, and economic modelling indicates such screening is cost-effective. Now that such screening is already underway in many countries, new data, along with the existing evidence, suggests opportunistic screening is the best way forward. More research is needed, however, on how best to screen and how to improve risk-factor control once dysglycaemia is detected.

Keywords Cardiovascular disease · Diabetes mellitus · Hospitalisation · Mortality primary care · Screening

Abbreviations

ABPI Ankle–brachial pressure index
ADDITION Anglo–Danish–Dutch study of intensive treatment in people with screen-detected diabetes in primary care

CVD Cardiovascular disease
GDM Gestational diabetes mellitus
IFG Impaired fasting glucose
IGT Impaired glucose tolerance

Introduction

Screening for undiagnosed disease remains a ‘hot topic’. Discussions continue over screening for various conditions; from cancer, with the risk of potentially harmful interventions in the falsely diagnosed, to gestational diabetes mellitus (GDM) and the need to balance diagnostic criteria with medicalising pregnancies, workload, and benefits to the mother and baby. In 2008, the growing importance of genomics, and the need to consider education and informed choice, led the World Health Organization to revise the original 1968 Wilson–Jungner’s criteria to justify the introduction of systematic screening [1]. There has been a longstanding question mark over the effectiveness of systematic screening for type 2 diabetes, or whether to continue with case finding at times of hyperglycaemic symptoms or potentially diabetes-related events. Screening for diabetes responds to a recognised need to reduce the current high risk of complications. The objectives of screening are clear, as earlier management may prevent or delay the onset of diabetes and, therefore, its complications. However, there have been two main gaps in the evidence: whether screening is effective for improving outcomes and, if so, whether the benefits outweigh any harm. ‘Harms’ relate more to health service costs and potential impact of increased personal health insurance rather than psychological harm, which has been shown to be unlikely [2].

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Evidence from diabetes screening studies

A systematic review in 2014, to update the 2008 US Preventive Services Task Force recommendations [3], concluded that, while treatment for impaired fasting glucose (IFG)/impaired glucose tolerance (IGT) delayed progression to (type 2) diabetes, screening for diabetes did not improve mortality rates. This conclusion was based upon two studies: (1) the Anglo–Danish–Dutch study of intensive treatment in people with screen-detected diabetes in primary care (ADDITION)–Cambridge trial ($n = 16,047$; high risk men and women, aged 40–69 years; 10 year duration) [4], with a mortality HR of 1.06 (95% CI 0.90, 1.25); and (2) the Ely trial ($n = 4936$; all men and women aged 40–65 years; 18 year duration) [5]. The Ely trial included a 1990–1999 cohort (HR 0.79 [95% CI 0.63, 1.00]) and a 2000–2008 cohort (HR 1.18 [95% CI 0.93, 1.51]). The Ely trial also compared clinical characteristics between those diagnosed with diabetes who were randomised to its screening ($n = 92$) and non-screening ($n = 60$) limbs over 12 years [6]. Besides a significantly higher ankle–brachial pulse index (also known as ankle–brachial pressure index [ABPI]) ($p = 0.035$) and a non-significant increase in retinopathy in the unscreened group (21% vs 35% [including one participant with proliferative retinopathy in the unscreened group]; $p = 0.08$), clinical characteristics were similar.

Simmons et al have now presented two additional controlled studies in this issue of *Diabetologia*, which investigated whether screening for type 2 diabetes, in asymptomatic individuals, is associated with a reduction in mortality [7, 8]. The studies were both part of the ADDITION-Europe study, but this time from the Danish limb (ADDITION-Denmark). One of these studies shows no reduction in mortality rate in participants in the screening programme vs the general Danish population [7], while the other [8] shows an association with participation in ADDITION and a significant reduction in adjusted HRs for all-cause mortality (0.79 [95% CI 0.74, 0.84]), cardiovascular mortality (0.80 [95% CI 0.72, 0.88]), cancer mortality (0.83 [95% CI 0.77, 0.89]) and diabetes-related mortality (0.66 [95% CI 0.54, 0.81]). The second study [8] also showed an association with a significant reduction in cardiovascular disease (CVD) events HR (0.84 [95% CI 0.80, 0.89]). Another study, by Feldman et al, also shows reduced all-cause mortality, cardiovascular disease, renal disease and retinopathy [9] among those who were screened and had their diabetes diagnosed early. What are we to make of these discordant findings? Do the latter studies provide evidence that we should screen asymptomatic individuals for diabetes and, if so, who should this include and how should we screen?

Limitations of ADDITION

We would suggest that, unfortunately, none of the studies has been designed adequately to test whether we should screen asymptomatic individuals for diabetes. Only the Ely and ADDITION-Cambridge studies included unscreened, randomly-selected control participants, at least allowing a properly controlled comparison of outcomes. In contrast, the ADDITION-Denmark studies were non-randomised and compare mortality (and cardiovascular events) only among those with diabetes, excluding any benefits among those identified with IFG and/or IGT. Furthermore, comparing patients in practices who agreed to participate in a trial (i.e. participants of ADDITION-Denmark) with those in practices who were not invited or declined to take part (a proportion of the ADDITION-Denmark control participants) is particularly fraught with selection bias, as general practitioners who are interested in diabetes achieve better diabetes outcomes than those less interested [10]. The ADDITION-Cambridge and Ely studies both overcame this problem by including randomised practices, or randomised individuals within a single practice, respectively. However, both of these UK-based studies included only a small number of participants with diabetes; the ADDITION-Cambridge study was carried out across multiple practices but only a small proportion ($n = 466$ or 3%), actually had screen-detected diabetes [4]. Similarly, the Ely study included only 2699 screened participants over 12 years, with 199 (7%) having newly-detected diabetes. The work by Feldman et al, suffered from the usually inherent potential selection biases.

The Ely study differed to the ADDITION studies in that all participants underwent an OGTT at baseline. ADDITION included a less comprehensive screening approach, using a risk calculator, then random capillary HbA_{1c} and glucose measurements using point of care meters, followed by a capillary fasting glucose test. Subsequently, an OGTT was carried out if screening was ‘positive’ by study criteria. The screened cohort in the Ely trial also had the OGTT repeated after approximately 5 years, while the ADDITION studies were based upon a single round of screening. Participant characteristics in each study therefore differed.

The impact of post-screening management on diabetes outcomes

Once diagnosed, a key factor determining mortality among those with diabetes is the intensity of the management received. Indeed, the ADDITION-Europe study was designed to compare the effect of intensive management with usual care for such patients, and after 5 years [11], overall it was found

that intensive management was associated with only a small non-significant reduction in the incidence of cardiovascular events and death (HR 0.91 [95% CI 0.69, 1.21]). However, there were substantial site differences, with a significant reduction in all-cause mortality across the two UK cohorts (Cambridgeshire and Leicester; HR 0.59 [0.35, 0.98]) but not in the Danish cohort. Danish healthcare differs to the English National Health Service and is ranked lower than the UK (as a whole) in a comparison of selected diabetes outcomes across the Organisation for Economic Co-operation and Development (OECD) [12]. This suggests that differences in care delivery may explain some of the differences in findings between ADDITION sites. Cambridgeshire (where both the ADDITION-Cambridge and Ely studies were undertaken) had patchy quality in local diabetes care and, hence, outcomes may have been even better with a more integrated approach to care [13]. However, overall, target achievement was only slightly greater in the practices that offered intensive intervention, so it may be that the intensive management plan used was insufficient to achieve a difference in CVD events vs control participants. We also know that intensive management takes time to achieve significant differences in mortality rates [14] and the ADDITION study may have been too short.

Conversely, overly intensive glycaemic management of type 2 diabetes is associated with increased mortality, albeit with reduced CVD events [15]. Since these screening trials were undertaken, diabetes treatment now includes agents that are associated with lower mortality (as determined by RCTs) [16, 17]; hence, outcomes would be expected to be better if such new agents had been available at the time of the studies (and used appropriately).

Of course, diabetes management also involves aggressive management of cardiovascular risk factors, particularly dyslipidaemia and hypertension, which, as shown by these new ADDITION data, are more rapidly accessed in screen-detected diabetes [7]. Access to the appropriate pharmaceutical agents and use of appropriate therapeutic targets, with minimal clinical inertia, would, therefore, be required in any trial testing the effectiveness of screening for diabetes. This requirement was not a component of the Ely study.

Designing future trials of diabetes screening

As a result of the evidence to date, the design of any new RCT in diabetes screening must include a plan for treatment of any participants that are newly-diagnosed with IFG, IGT or diabetes in the study. In line with this, ethical considerations now prevent the use of blinded OGTTs or screening tests at

Lessons from diabetes screening studies

- 1 Treating hyperglycaemia in type 2 diabetes from diagnosis reduces micro- and macrovascular outcomes and mortality over 10 years [14]
- 2 Managing IFG/IGT reduces progression to type 2 diabetes over 15 years [18]
- 3 Intensive management of screen-detected diabetes reduces incidence of cardiovascular events and death over 5 years in the UK [11]
- 4 In the Ely trial, testing for diabetes using an OGTT with repeated OGTT after 5 years was associated with non-significant reductions in all-cause mortality, significantly lower ABPI and non-significantly reduced rates of retinopathy in those in the screening group who were diagnosed with diabetes vs unscreened individuals [5, 6]
- 5 In the 2015 US Preventive Services Task Force systematic review, all seven health economic modelling studies reported screening (vs no screening) at age 40–45 is associated with incremental cost-effectiveness ratios of < \$15,000/quality-adjusted life year (QALY), which is well under the traditional thresholds for cost-effectiveness [3]

the commencement of any trial. Because of this, the design of future RCTs in diabetes screening would require randomisation to either a screened or unscreened cohort (as per ADDITION-Cambridge). The numbers required for such a trial have now been calculated by Echouffo-Tcheugui and Prorok [19], based on ADDITION and other studies. They show that the number of people needed in each arm of a 10 year diabetes screening trial among adults aged 55–64 years, with 80% power to show a 15% reduction in mortality, would be 306,356.

Furthermore, such a trial may no longer be viable in many countries that have now adopted national screening and prevention programmes (e.g. the UK), in which the yield of unscreened individuals with undiagnosed diabetes may be low. This may be the case particularly among women, many of whom, with [20] or without [21] diabetes risk factors, will now be screened for GDM using a blood test. In fact, the proportion of individuals with undiagnosed diabetes seems to be dropping already. For example, the latest UK modelling suggests that only 25% of those with diabetes are now undiagnosed [22], half of the 50% quoted historically. This

is likely to be the result of opportunistic screening in primary care. These developments increasingly suggest that both policy makers and primary care practitioners believe that equipoise has now been reached for screening for undiagnosed diabetes, and the only questions that remain are who and how to screen. Whether to use a risk score followed by a ‘blood test’, or universal screening with a ‘blood test’ at, for example, 40–45 years of age, remains open. The use of a combination of random glucose levels (5.5–11.0 mmol/l) with an $\text{HbA}_{1c} \geq 6.1\%$ (43 mmol/mol), as used by ADDITION, is one approach to decide who should proceed to the next test of either fasting glucose alone, OGTT or HbA_{1c} . The substantial problems with HbA_{1c} analysis, a test that is significantly influenced by the lifespan of the red blood cell, are that it generates multiple false positive and false negative tests [23], and is poor at detecting IGT/IFG without use of a low threshold (5.7% [40 mmol/mol]) [24], suggesting that HbA_{1c} should not be used alone for screening for diabetes. A trial comparing different screening strategies, with different expected uptake (higher for random blood glucose and HbA_{1c} than fasting blood glucose or OGTT) and sensitivities, may be the next step in countries with national prevention/screening programmes already in place. Countries with national records, such as Sweden, would be ideal for such a study.

A trial of screening may be feasible and ethical in populations where the incidence of type 2 diabetes is high, the incidence of diabetes complications is also high (e.g. many non-European populations) and access to screening and quality diabetes care (once diagnosed) is limited. Such a trial could use a stepped-wedge cluster design [25], so that all participating communities would gain access to the intervention over time, including strategies to optimise care quality. There would need to be a commitment to establishing a sustainable screening and management programme for those with existing diabetes beyond the life of the trial and an associated prevention programme for those with IGT/IFG would need to be introduced. The power calculations of Echouffo-Tcheugui and Prorok would need to be reviewed, with a potential for the required numbers to be reduced as they are based upon European populations with lower prevalence of diabetes and complication rates, although this may be mitigated by the falling CVD rates with modern therapy. Even so, this would require substantial investment in both materials and staff, and must be able to fit into the existing healthcare system.

Conclusions

In conclusion, trials of screening for undiagnosed diabetes among asymptomatic individuals may no longer be feasible or ethical in many countries. The most efficient

recommendation may be opportunistic screening [26], where patients already seeking care (including screening) for another condition are subsequently tested for diabetes or IGT/IFG. If screened positive, they are more likely to receive treatment, thus leading to improved outcomes. There is probably sufficient evidence to conclude that this systematic approach to screening should occur in primary care (i.e. not through a centralised approach, as occurs for some cancers) and that focus should now shift to trials of how to screen, methods for implementing treatment earlier, and better risk factor control in those at highest risk.

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