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Does addressing prediabetes help to improve population health?

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The concept of prediabetes has been much debated. One view is that recognition of this condition could help to boost efforts to reduce the future burden of diabetes and its complications. The counterargument is that describing people with an increased risk of type 2 diabetes as having prediabetes creates more problems than benefits in terms of prevention and treatment; eg, unnecessary medicalisation and an unsustainable burden on health-care systems.

Prediabetes develops when insulin-producing cells in the body are unable to produce enough insulin for a given level of insulin resistance. This situation leads to prediabetes states such as impaired fasting glucose, impaired glucose tolerance, or raised HbA_{1c}, in which blood glucose concentrations are higher than normal, but lower than those defining diabetes.[1] Prediabetes increases the risk of diabetes,[2] but both prediabetes and diabetes might also revert to normoglycaemia, as shown in lifestyle and drug-based intervention trials and studies of the outcomes of bariatric surgery.[1,3,4]

In *The Lancet Diabetes & Endocrinology*, Mohammed Ali and colleagues[5] report on trends in cardiovascular and renal burdens of people with prediabetes in the USA from 1988 to 2014, using data from the US National Health and Nutrition Examination Surveys (NHANES). NHANES is a programme of population-based studies designed to assess the health of adults and children in the USA. Ali and colleagues did an analysis of NHANES data from consecutive, representative cross-sectional studies of non-pregnant adults aged 20 years and older obtained during 1988–94, 1999–2004, 2005–10, and 2011–14.[5] They estimated, based on the most inclusive definition of prediabetes, that the number of Americans with prediabetes (ie, fasting plasma glucose [FPG] 100–125mg/dL or HbA_{1c} 5·7–6·4%) increased from 56·2 million during 1988–94 to 78·5 million during 2011–14. When a more stringent definition of prediabetes was used (FPG 100–125mg/dL plus HbA_{1c} 5·7–6·4%), the corresponding increase was from 12·1 million to 19·5 million. In 2011–14, prediabetes status was accompanied by multiple risk factors and disorders, including hypertension (36·6% [95% CI 32·8–40·5]), dyslipidaemia (51·2% [47·0–55·3]), albuminuria (7·7% [6·8–8·8]), and reduced estimated glomerular filtration rate (4·6% [3·7–5·9]).

Compared with participants with diagnosed diabetes, individuals with prediabetes received less treatment. This was particularly true in the case of lipid lowering—only about 40% of participants with prediabetes and dyslipidaemia were treated, whereas more than 70% of patients with diagnosed diabetes and dyslipidaemia received lipid-lowering treatment. The authors' conclusion, based on all these findings, is that identifying prediabetes might open up valuable opportunities to improve the health of the population.

Observational epidemiological studies in the USA, such as Framingham research, the Atherosclerotic Risk in Communities study, and NHANES, have been very useful for the identification of associations between risk factors and chronic diseases. Ali and colleagues' analysis provides valuable information about secular trends in the key risk factors for diabetes in the USA. However, any public health implications should be considered in the context of interventional evidence.

Whether addressing prediabetes would make a significant contribution to the prevention of

cardiovascular disease is currently unclear. Targeting individuals with prediabetes with a 6-year lifestyle intervention programme reduced the incidence of cardiovascular mortality over 25 years of follow-up in the small (n=577) Chinese Da Qing Diabetes Prevention trial.[6] These findings might not be generalisable to European and American populations in view of the very different prevention contexts. Although almost 50% of Chinese adults have hypertension, less than a third are being treated, and fewer than one in 12 are in control of their blood pressure.[7] According to NHANES, however, almost 80% of people in the USA with hypertension are treated.[5] In this context of more effective population-level prevention of cardiovascular disease, neither additional lifestyle intervention nor metformin in prediabetes had an effect on the aggregate microvascular outcome in the US Diabetes Prevention Program Outcome Study.[8] These findings were consistent with those reported from the large UK ADDITION-Cambridge trial,[9] which included more than 16 000 high-risk participants. In this study, neither screening for diabetes plus intensive multifactorial treatment for people diagnosed with diabetes, nor screening plus routine diabetes care according to national guidelines was successful in reducing 10-year mortality related to cardiovascular disease or diabetes compared with a reference group of patients who were not screened for diabetes but were treated in accordance with cardiovascular disease-prevention guidelines.

Some of the findings from Ali and colleagues' analysis imply that any additional cardiovascular benefits from specifically targeting individuals with prediabetes would be modest.[5] In the NHANES study, the 10-year risk of cardiovascular disease in 2011–14 according to the American Heart Association atherosclerotic cardiovascular disease risk calculator showed little difference between the people with prediabetes (6·9%, 95% CI 6·4–7·4) and those with normal glycaemic status (6·3%, 5·9–6·7). This was also the case for untreated dyslipidaemia and hypertension.

Lipid lowering by means of statin therapy is one of the cornerstones of cardiovascular-disease prevention in people with high or intermediate overall risk.[10] However, it is unknown whether the treatment targets for individuals with prediabetes should be as strict as for people with diagnosed diabetes, or more relaxed, as for the general population. A related uncertainty is that statins are associated with a modestly increased risk of diabetes,[11] a potential harmful effect with particular relevance for individuals with prediabetes, for whom even a slight increase in glucose concentrations might be enough to cross the diagnostic threshold for diabetes.[11,12] Current opinion is that the benefits of using statins to reduce LDL cholesterol concentrations and the risk of cardiovascular disease outweigh any harmful effects.[13]

Although the benefits of addressing prediabetes in attempts to prevent cardiovascular disease seem modest, this is not the case for diabetes prevention. Several trials, including the US Diabetes Prevention Program Outcomes Study,[8] have shown that intensive lifestyle modification can significantly reduce or delay the onset of diabetes in people with impaired glucose tolerance.[1,8] Targeting this group will therefore benefit public health. However, the enormous number of affected people in the USA and elsewhere might overwhelm health-care systems, leading to less-than-optimal efficiency in terms of preventive efforts. The findings reported by Ali and colleagues[5] could help to resolve this issue in showing a persistent clustering of prediabetes with other factors that increase the risk of diabetes.[1] Further research could build on this clustering to develop multifactorial risk-prediction algorithms that allow the identification of a more restricted target population including only individuals who are at the highest risk of developing diabetes within a population of people with prediabetes.

Mika Kivimäki, Adam G Tabák
Department of Epidemiology and Public Health, University College London, London, WC1E6BT, UK (MK, AGT); Clinicum, Faculty of Medicine, University of Helsinki, Finland (MK); and Semmelweis University Faculty of Medicine, 1st Department of Medicine, Budapest, Hungary (AGT)
m.kivimaki@ucl.ac.uk

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Renal trials in diabetes need a platform: time for a global approach?

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Renal morbidity and mortality in patients with diabetes is high, and although angiotensin-receptor blockers have been successful in reducing morbidity and mortality, the residual risk remains elevated. Patients who do not respond to the prescribed drugs contribute substantially to this unmet need. This variation in therapy response is in part due to heterogeneity in the causes of renal disease progression in patients with diabetes.[1] To increase the therapeutic options available, research has focused on pathways beyond the renin–angiotensin system (RAS). Several drug targets have been tested by evaluating efficacy of drugs to improve surrogate markers such as blood pressure, blood glucose concentration, cholesterol, HbA_{1c}, and albuminuria. Many promising drugs were discovered, which appeared to be particularly effective in reducing albuminuria. Unfortunately, only a few have reached the stage of trials assessing hard outcomes. This high attrition rate is not only due to scarce funding for large, expensive, hard outcome trials, but also the fact that each new drug must be tested separately through to phase 4 trials. To date, at least three promising drugs have advanced to the final stage of development: atrasentan (SONAR; NCT01858532), canagliflozin (CREDENCE; NCT02065791), and finerenone (FIDELIO; NCT02540993).

These trials are expected to show that the drug will delay the progression of renal disease on top of current guideline therapy. The outlook is promising for all three drugs; however, no matter how good the outcome, none of these drugs will give protection to all patients. This expected variation in therapy response is supported by the fact that each of these drug classes has shown a variable effect on the important surrogate outcome albuminuria (figure). If this variability translates into variation in hard renal outcomes, it would mean that each trial will have a large group of patients who do not benefit from the drug. A substantial residual risk is, therefore, likely to remain after completion of all three trials.

Far more important than the success of each of these three trials individually is that the results will not answer the question of what to do with the non-responders from each trial. The individual trials will answer whether a non-responder to RAS-intervention has benefited from the new drug, but not whether a non-responder might benefit from one of the other two drugs. Another key question that these trials will not answer is whether the three drugs induce responses only in the same patients, or if each drug provides benefit for a discrete patient population. In the best case scenario of three positive trials resulting in three new protective mechanisms, we could be left with the frustration of having identified three discrete groups of non-responders to single agents, but being deprived of the means to test their response to the other promising alternatives.

The design of studies in this area should be changed to overcome this hurdle, and to get answers about how to deal with responders and non-responders. Directly selecting patients with a positive surrogate marker response to a drug into trials of that drug, as well as de-selecting patients with a negative surrogate marker