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**Does addressing prediabetes help to improve the health of the population?***Mika Kivimäki\*, Adam G. Tabak*

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The concept ‘prediabetes’ has been much debated. One view is that it provides potentially useful information that could boost efforts to reduce the future burden of the disease. The counterargument is that describing people with an elevated risk of type 2 diabetes as pre-diabetic creates more problems than benefits in terms of prevention and treatment. In this issue of *Lancet Diabetes & Endocrinology*, Ali and colleagues report on prediabetes trends in the United States over the last 25 years using data from the *National Health and Nutrition Examination Survey (NHANES)*.<sup>1</sup> Their conclusion, based on this extended follow-up, is that identifying prediabetes may open up valuable opportunities to improve the health of the population.

Prediabetes develops when the insulin-producing cells in the body are unable to produce enough insulin for a given level of insulin resistance. This leads to pre-diabetes states such as impaired fasting glucose, impaired glucose tolerance or raised HbA1c, in which blood-glucose concentrations are higher than normal, but lower than those defining diabetes.<sup>2</sup>

Prediabetes increases the risk of diabetes,<sup>3</sup> but both prediabetes and diabetes may also convert back to normoglycaemia, as shown in lifestyle and drug-based intervention trials and studies on the outcomes of bariatric surgery.<sup>2,4,5</sup>

NHANES is a programme of population-based studies designed to assess the health of adults and children in the United States. For the current analysis, Ali and colleagues used NHANES data from 1988-1994, 1999-2004, 2005-2010 and 2011-2014.<sup>1</sup> They estimated, based on the most inclusive definition of prediabetes, that the number of pre-diabetic Americans aged 20 years and older increased from 56.2 million at the time of the first examination to 78.5 million at the time of the last one. The corresponding increase was from 12.1 million to 19.5 million when the most stringent definition of prediabetes was used. In addition, prediabetes was accompanied with multiple risk factors and disorders: more than half had dyslipidaemia (as indicated by the lipid goals for diabetic individuals), one in three were hypertensive and one in ten had kidney problems. Compared to US adults with diagnosed diabetes, individuals with prediabetes experienced poorer treatment rates. This was particularly true in the case of lipid-lowering: only 40 per cent of pre-diabetic adults with dyslipidaemia were treated, whereas the corresponding proportion among those with diagnosed diabetes was more than 70 per cent.

Observational epidemiological studies in the US, such as Framingham' research, the Atherosclerotic Risk in Communities (ARIC) study and NHANES, have been extremely useful in identifying the associations of risk factors with chronic diseases. The current analysis conducted by Ali and colleagues provides valuable information about secular trends in the key risk factors of diabetes in the USA. However, any public-health implications should be considered in the context of interventional evidence.

It is currently unclear whether addressing prediabetes would make a significant contribution to preventing cardiovascular disease. Targeting pre-diabetics with a

six-year lifestyle intervention programme reduced the incidence of cardiovascular mortality over 25 years of follow-up in the small Chinese Da Qing Diabetes Prevention trial (N=577).<sup>6</sup> However, these findings may not be generalizable to the Western world given the very different prevention contexts. Although almost 50 per cent of Chinese adults have hypertension, fewer than a third are being treated, and fewer than one in 12 are in control of their blood pressure.<sup>7</sup> According to NHANES, on the other hand, almost 80 per cent of US persons with hypertension are treated, and the corresponding treatment rate is >90 per cent among those with diagnosed diabetes.<sup>1</sup> It is therefore not surprising that neither lifestyle intervention nor metformin in pre-diabetic people had an overall effect on the aggregate microvascular outcome in the Diabetes Prevention Program Outcomes Study, which was carried out in the US context of more effective population-level cardiovascular-disease prevention.<sup>8</sup> These findings are consistent with those reported from the large UK ADDITION-Cambridge trial, including more than 16,000 high-risk participants. In the latter 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 cardiovascular or diabetes-related mortality compared to a reference group not screened for diabetes but treated according to cardiovascular-prevention guidelines.<sup>9</sup>

Some of the findings from the analysis conducted by Ali and colleagues also imply that any additional cardiovascular benefits from targeting specifically pre-diabetic individuals would be modest.<sup>1</sup> In the NHANES study, for example, the 10-year risk of cardiovascular disease according to the ASCVD Risk Estimator showed little difference between the group of people with prediabetes (6.9%) and those with a normal glycaemic status (6.3%). This was also the case for the rates of untreated dyslipidaemia and hypertension.

Lipid-lowering by means of statin therapy is one of the cornerstones of cardiovascular-disease prevention among people with high or intermediate overall risk.<sup>10</sup> However, it is not currently known whether the treatment targets for individuals with prediabetes should be as ambitious as for people with diagnosed diabetes, or more relaxed as is the case with the general population. A related uncertainty reflects the fact that statins are associated with a modestly increased risk of diabetes, a potential harmful effect with particular relevance to pre-diabetic individuals for whom even a slight increase in glucose concentrations may be enough to cross the diagnostic threshold for diabetes.<sup>11,12</sup> Current opinion is that the benefits of using statins to reduce LDL concentrations and the risk of cardiovascular disease outweigh any harmful effects.<sup>13</sup>

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, have demonstrated that intensive lifestyle modification can significantly reduce or delay the onset of diabetes among those with prediabetes.<sup>2,8</sup> Targeting this group will therefore benefit public health. However, the enormous number of affected people in the US and elsewhere may overwhelm healthcare systems, leading to less-than-optimal efficiency in terms of preventive efforts. The findings reported by Ali and colleagues could help to resolve this issue in showing a persistent clustering of prediabetes with other factors that increase the risk of diabetes.<sup>1</sup> 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 the group of pre-diabetic people.

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