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LETTER

Environmental exposures are important for type 2 diabetes pathophysiology in sub-Saharan African populations

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Abbreviations
SSA Sub-Saharan Africa
TB Tuberculosis

To the Editor: We have read with great interest the comprehensive and ambitious review on the pathophysiology of type 2 diabetes in individuals from sub-Saharan Africa (SSA) by Goedecke and Mendham, published in *Diabetologia* [1]. The authors discuss pathophysiological mechanisms in the pathogenesis of insulin resistance and type 2 diabetes, with an emphasis on the role of adipose tissue and ectopic fat, as well as sex differences. The authors call for longitudinal and intervention studies, of which there are very few involving Black African individuals in the current context, and we applaud them for raising awareness of such initiatives. These studies are particularly required in relation to insulin secretion, clearance and sensitivity in this population as a result of interventions including exercise, nutrition and/or body weight change.

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While the review by Goedecke and Mendham discusses some environmental aspects of type 2 diabetes risk, including infections and epigenetics [1], these were not discussed as rigorously or in as much detail as were aspects of so-called 'lifestyle interventions'. In our view, the impact of infectious diseases and fetal programming by epigenetics need to be discussed in much more detail as such environmental aspects are likely to be common in African populations, and may, therefore, confound results obtained by future lifestyle intervention studies [2].

We propose that infectious diseases, such as tuberculosis (TB) with or without co-infection with HIV, in sub-Saharan African populations should be emphasised more with regard to the risk of developing type 2 diabetes. Every year, the SSA region contributes to ~30% of the total number of global TB cases (~10 million cases), and it is estimated that the annual number of TB/HIV cases is 600,000, which is equivalent to three-quarters of the global estimate [3]. For various reasons, in sub-Saharan Africans there is a considerable delay in TB diagnosis. This delay in diagnosis contributes to persistent inflammation, which partly affects pancreatic beta cells and, which in the pancreatic islets, results in infiltration of immune cells, increased proinflammatory cytokines and chemokines, apoptosis, and amyloid deposits that induce fibrosis and, at least in part, pancreatic beta cell dysfunction [4, 5]. Hyperglycaemia is a common phenomenon in individuals with TB, with 50% of those infected being found to have persistent dysglycaemia despite receiving anti-TB treatment [6]. Furthermore, HIV has been recognised as a dominant risk factor for persistent dysglycaemia in individuals treated for TB [6]. Stress from severe chronic infection is likely to enhance insulin resistance in key tissues (liver, skeletal muscle etc.) and unmask an underlying beta cell deficiency, leading to chronic hyperglycaemia. Thus, the increased risk of type 2 diabetes among people with TB is plausible [7]. Longitudinal studies aiming to estimate incidence of type 2 diabetes in individuals with TB-induced

hyperglycaemia are, therefore, essential to guide strategies for the prevention and control of type 2 diabetes in order to reduce the risk of increasing the proportion of manifest type 2 diabetes in Africa. Figure 1a provides a visual overview of the association between TB and type 2 diabetes.

In their review article, Goedecke and Mendham write that DNA methylation is reversible [1]. This is only partly true and it is important to state that some epigenetic patterns and modifications can be irreversible. This has been demonstrated in several epidemiological studies that included cohorts from the Dutch famine winter, in which conservation of DNA methylation was demonstrated in offspring after 60 years of follow-up [8]. In addition, it is known that low and high birthweight are both associated with changes in the degree of DNA methylation as compared with normal birthweight, but it is unclear as to whether these epigenetic modifications are stable or dynamic over life [9]. Birthweight is highly linked to maternal nutrition and placental growth. For example, diabetes in pregnancy is associated with increased fetal nutrient supply owing to increased transfer of glucose and NEFAs across the placenta, which give rise to larger birthweight [9]. It remains largely unknown, however, how much birthweight- and maternal nutrition-associated epigenetic changes play a role in an African context. However, we recently documented in a rural Tanzanian population study cohort that anaemia in pregnancy, mainly caused by iron deficiency, leads to distinct DNA methylation and gene expression patterns in cord blood of offspring [10]. Notably, it is necessary to continue studying the effect of these epigenetic changes on offspring risk of developing type 2 diabetes and other cardio-metabolic diseases later in life. Indeed, widespread dietary challenges during pregnancy in the African continent may, in part, be linked to cardio-metabolic diseases later in life, potentially through epigenetic changes arising in utero [9]. Figure 1b provides a visual overview of the association between epigenetic changes and type 2 diabetes.

Furthermore, there is evidence that gestational diabetes is a risk factor for having manifest diabetes, not only for the mother but also for the offspring [11]. We recently found a gestational diabetes prevalence of 39% in 392 women in rural Tanzania [12], indicating that metabolic challenges during pregnancy in SSA may be an important underlying factor for the risk of developing type 2 diabetes at the population level.

SSA is a region where prevention and early diagnosis of hyperglycaemia is a challenge and needs higher prioritisation to avoid secondary, as well as tertiary prevention due to late diagnosis. We appreciate the efforts made by Goedecke and Mendham to give an overview of the pathophysiology of type 2 diabetes in sub-Saharan Africans [1]. Our follow-up is meant as an addition to the points made in their review, to

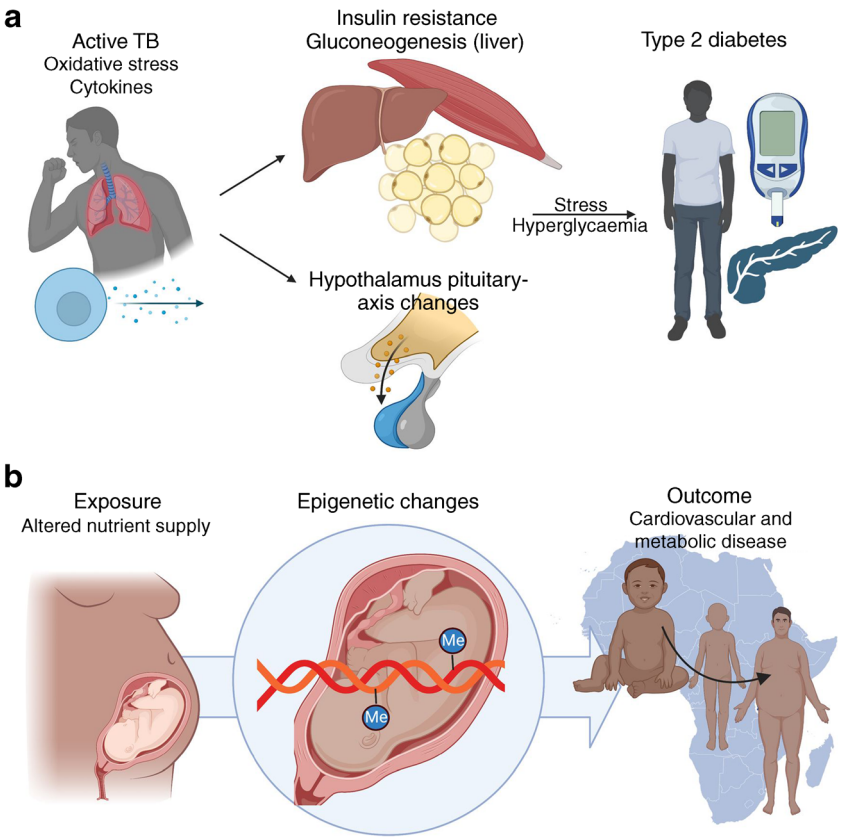

Fig. 1 The development of type 2 diabetes via (a) active TB and (b) epigenetic changes in fetal life. Me, methylation

add important information to the complex topic of the development of type 2 diabetes in SSA.

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