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LETTER

Environmental exposures are important for type 2 diabetes pathophysiology in sub-Saharan African populations. Reply to Christensen D, Hjort L, Mpagama S et al [letter]

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Abbreviations

GDM	Gestational diabetes
SSA	Sub-Saharan Africa
TB	Tuberculosis

To the Editor: We would like to thank Christensen et al [1] for their thoughtful letter in response to our review on the pathophysiology of type 2 diabetes in sub-Saharan Africans [2]. Christensen et al [1] correctly highlight that aspects of infectious diseases and fetal programming by epigenetics were not discussed in depth in the review. This was certainly not due to their relative importance but merely due to word limitations and the scarcity of relevant mechanistic studies undertaken in sub-Saharan Africa (SSA).

Tuberculosis (TB) is the leading cause of deaths owing to infectious disease globally, and a quarter of TB cases in 2020 were from SSA [3]. Christensen et al [1] propose how delayed TB diagnosis in SSA may contribute to persistent inflammation that may eventually lead to beta cell dysfunction and increase the risk for type 2 diabetes. While this is an attractive hypothesis, there is little supporting evidence. In a meta-analysis of TB-associated hyperglycaemia including many studies from SSA, Menon et al [4] reported that hyperglycaemia may occur in ~10% of TB patients at diagnosis. It has been proposed that this is likely due to the stress response related to TB infection [5], which resolved in ~50% of patients after 3–6 months of TB treatment [4]. However, longer duration of follow-up is required to assess whether the transient hyperglycaemia observed with TB progresses to overt type 2 diabetes [4, 5].

While the evidence linking TB to type 2 diabetes risk is inconclusive, there is consistent evidence, mainly from high-income countries, to show that type 2 diabetes is associated with an increased risk of developing latent and active TB [6]. Even though the evidence from SSA is scarce, a recent systematic review including studies from SSA (n=9) reported a 2.8-fold (95% CI 1.9, 4.1) higher risk for TB among those with type 2 diabetes than without [7]. This estimate appears slightly higher than that reported in global reviews [6], possibly attributed to poorer glycaemic control in individuals from SSA. Nonetheless, individuals with TB and type 2 diabetes have a greater predisposition to treatment failure, infection relapses and increased mortality [8]. Hence, an improved understanding of the bidirectional relationship between TB and type 2 diabetes is essential to prevent the dual burden and associated morbidity and mortality.

Type 2 diabetes has also been shown to increase susceptibility to other infectious diseases such as malaria. SSA carried the burden of malaria cases and deaths in 2020 (95% and 96% of global cases and deaths, respectively) [9]. Studies have shown an increased risk for *Plasmodium falciparum* (malaria) infection in individuals with type 2 diabetes, with the risk and virulence of the infection increasing with

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increasing blood glucose concentrations [10, 11]. Hence, with the increasing rise in projected rates of type 2 diabetes in SSA [12], the already high burden of infectious diseases will be exacerbated.

In addition to the high prevalence of infectious disease, SSA is grappling with a high burden of obesity that is impacting women of reproductive age [13]. Consequently, pregnancies in SSA are often complicated by obesity and obesity-related conditions, such as gestational diabetes (GDM), as highlighted by Christensen et al [1]. A meta-analysis on the prevalence of GDM in Africa estimated a pooled prevalence of 14.3% in SSA [14]. The impact of GDM on type 2 diabetes burden was illustrated by a study conducted in South Africa where about one-third of women with GDM developed type 2 diabetes within 5–6 years postpartum [15]. Further, children born to women with GDM are more likely to develop type 2 diabetes later in life, thus enabling the perpetuation of the type 2 diabetes burden in the next generation, most likely through epigenetic mechanisms [16]. Indeed, a recent study conducted in South Africa reported epigenetic alterations in the blood of pregnant women and in the placental tissues of fetuses, resulting in reductions in the expression of glucose 6-phosphate dehydrogenase and genes encoding insulin-like growth factor-binding proteins, respectively [17]. This study proposed a pathophysiological link between these epigenetic modifications, adverse pregnancy outcomes and fetal macrosomia. Other studies have similarly reported altered epigenetic marks in South African women with GDM [18–21]. Although these studies did not measure the epigenetic profiles of the children, they showed that HIV modifies the epigenetic profiles of women with GDM [18, 21]. Accordingly, further studies are required to examine the epigenetic underpinnings of GDM on type 2 diabetes risk in the mother and offspring in SSA. It is essential that these studies explore interactions with infectious diseases such as HIV, as ~30% of all pregnant women in South Africa are living with HIV [22].

Notably, there are ongoing cohort studies in SSA that are observing the life trajectories of mothers and their children that may be harnessed to explore the epigenetic mechanisms that may lead to type 2 diabetes. Examples of these studies include the Epigenetic Mechanisms linking Pre-conceptional nutrition and Health Assessed in India and SSA (EMPHASIS) study [23], Birth to Twenty plus (Bt20+) [24], the Healthy Life Trajectories Initiative (HeLTI) [25], the Drakenstein Child Health Study (DCHS) [26], the Foetal Exposure and Epidemiological Transitions: the role of Anaemia in early Life for Non-Communicable Diseases in later life (FOETALforNCD) study [27], the Hormonal and Epigenetic Regulators of Growth (HERO-G) study [28], as well as the Obesogenic Origins of Maternal and Child Metabolic Health Involving Dolutegravir (ORCHID) study that is exploring the interactions between metabolic health, HIV and antiretroviral therapy (ClinicalTrials.gov registration no. NCT04991402). However, these studies are focused exclusively on maternal exposures. More recently, the Developmental Origins of Health and Disease (DOHaD) hypothesis was extended to include the Paternal Origins of Health and Disease (POHaD) paradigm, with prenatal exposures to parental smoking being linked to a greater risk of overweight, obesity and type 2 diabetes [29, 30]. Understanding the paternal role on type 2 diabetes risk in offspring will pose a challenge in the SSA context due to the complex social environment and the preponderance of female-headed homes [31].

In addition to the comments made by Christensen and colleagues [1], countries across SSA are at different stages of nutrition transition and economic development, which creates diversity in environmental and lifestyle exposures that have an impact on regional variability in the prevalence of communicable and non-communicable disease risk ([12, 14, 32–34]). These exposures may include malnutrition, environmental chemicals, maternal stress and infectious diseases, which may directly and/or indirectly impact on the pathophysiological mechanisms of type 2 diabetes risk in SSA [35–37]. Although the mechanisms between these lifestyle factors and type 2 diabetes risk have been recently reviewed [35], the lack of data from SSA is obvious and warrants further investigation.

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