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## Age of onset of diabetes and all-cause mortality

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### Abstract

Diabetes mellitus continues to present a large social, financial and health system burden across the world. The relationship between age of onset of the different types of diabetes and all-cause mortality is uncertain. In this review paper, the relationship between age of onset of the different types of diabetes and all-cause mortality will be reviewed and an update of the current evidence will be presented. There is strong evidence of the relationship between age of onset of type 2 diabetes mellitus (T2DM) and all-cause mortality, good evidence of the relationship between age of onset of T1DM and all-cause mortality and no evidence of the relationship between age of onset of gestational diabetes or prediabetes and all-cause mortality. Further research is needed to look at whether aggressive management of earlier onset of T2DM can help to reduce premature mortality.

**Key words:** Diabetes mellitus; Age of onset; Mortality; Type 1 diabetes; Type 2 diabetes; Gestational diabetes; Prediabetes

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**Core tip:** In this review paper we will look at the relationship between age of onset of the different types of diabetes (type 1 diabetes mellitus, type 2 diabetes mellitus, gestational and prediabetes) and all-cause mortality and provides an update of the current evidence.

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## INTRODUCTION



Diabetes mellitus is potentially reversible<sup>[1-3]</sup> but the disease continues to present a large social, financial and health system burden across the world<sup>[4]</sup>. Lifetime cost of treating type 2 diabetes mellitus (T2DM) in has been estimated to range from USD 50000 to USD 130000 in United States of America<sup>[5]</sup> and SGD 70000 to SGD 130000 in Singapore<sup>[6]</sup> depending on age of diagnosis. A systematic review of population-based cohorts found excess mortality in type 1 diabetes mellitus (T1DM) diagnosed in childhood and adolescence<sup>[7]</sup>. Another systematic review also found that T2DM is associated with a two-fold increase in mortality<sup>[8]</sup>. In Hongkong, it was found that absolute and relative mortality has declined overall in diabetes patients but there is less marked improvement in patients under 45 years of age, implying a need to improve care in young onset diabetes patients<sup>[9]</sup>. What is uncertain is the relationship between age of onset of the different types of diabetes and all-cause mortality. This is important as American Diabetes Association recommends screening for T2DM to begin at 45 years for patients with no risk factors<sup>[10]</sup> while Singapore recommend screening starts at 40 years old with no risk factor<sup>[11]</sup>. If earlier onset of T2DM is associated with a much higher all-cause mortality, then we must relook at the screening criteria so that we do not miss out on these high-risk group. A better risk stratification model may be needed to ensure that earlier onset T2DM patients are not overlooked to reduce premature mortality.

In this review paper we will look at the relationship between age of onset of the different types of diabetes (T1DM, T2DM, Gestational and Prediabetes) and all-cause mortality and provides an update of the current evidence. This will help to inform readers of the need to pay special attention to the group of DM patients with early onset and not delay treatment unnecessarily.

## LITERATURE RESEARCH

A literature search was done as part of this narrative review which included electronic databases of PubMed and Google Scholar. Only English-Language original and review articles were reviewed. As no systematic review has been done on this topic due to insufficient original research studies, we decided to do a narrative review instead. Only relevant studies were included in this narrative review using search terms such as “Diabetes”, “Age of onset”, “Mortality” and “Death”.

## AGE OF ONSET OF T1DM

T1DM is most common in youth, accounting for more than 85% of all diabetes case below 20 years of age in the world<sup>[12,13]</sup>. A Swedish study found that patients who developed T1DM before 10 years of age had a three-fold increase in mortality compared to controls while those who developed T1DM between 26 to 30 years of age had less than two-fold increase in mortality compared to controls<sup>[14]</sup>. Another Finnish study found that the standardised mortality ratio was 3.6 in the early onset (0-14 years) cohort and 2.8 in the late onset (15-29 years) cohort<sup>[15]</sup>. However, an older study of 13 population-based EURODIAB registers in 12 countries did not find any significant difference in the standardised mortality ratios by age of diagnosis<sup>[16]</sup>.

Based on current evidence, it is probably worthwhile to delay the onset of T1DM if this was possible and there are some recent promising results that showed that it is possible to delay progression to clinical T1DM in high risk individuals<sup>[17]</sup>. However, routine screening for T1DM is not recommended<sup>[18,19]</sup> as there is no therapy currently proven to prevent or significantly delay the onset, so more research is needed in this area to warrant further discussion.

## AGE OF ONSET OF T2DM

T2DM which was previously diagnosed in adults is now affecting children<sup>[20]</sup> and adolescents. It has been found that T2DM presenting at a young age is of aggressive nature by the landmark Search for Diabetes in Youth study<sup>[13]</sup>. Furthermore, increased lifetime exposure to hyperglycaemia is likely to be associated with higher complication risks<sup>[21]</sup>. Two Australian studies found an inverse relationship between age of onset of Type 2 Diabetes and complication risk and mortality<sup>[22,23]</sup>. A Swedish study also found that patients with T2DM diagnosed below 40 years had the highest excess risk for all-cause mortality and interestingly patients with T2DM diagnosed after 80 years old had no excess mortality<sup>[24]</sup>.

Based on current evidence, it is likely that younger age of onset of T2DM is likely

associated with higher all-cause mortality and it is worthwhile to prevent or delay the onset of T2DM. Furthermore, it has been found that the younger age of onset of diabetes is associated with higher levels of lifetime excess medical spending attributed to diabetes both in United States<sup>[25]</sup> and Singapore<sup>[6]</sup>.

## AGE OF ONSET OF GESTATIONAL DIABETES

Gestational diabetes is defined as glucose intolerance that begins or is first recognized during pregnancy<sup>[26]</sup> and this is increasing in prevalence in tandem with increase in prevalence of overweight and obesity in women of reproductive age<sup>[27]</sup>. Although gestational diabetes is a strong risk factor for developing T2DM<sup>[28-30]</sup> in future, there are no studies that looked at the relationship between gestational diabetes and all-cause mortality. However, a recent systematic review found that young women with Gestational Diabetes have a twofold higher risk of cardiovascular events postpartum compared with their peers independent of the risk of developing T2DM<sup>[31]</sup>. Based on current evidence, little is known of the relationship between age of onset of Gestational Diabetes and all-cause mortality, so more research is needed in this area to warrant further discussion.

## AGE OF ONSET OF PREDIABETES

Prediabetes is an intermediate state of hyperglycaemia with glycaemic parameters above normal but below the diabetes threshold<sup>[32]</sup>. A systematic review found that impaired glucose tolerance or impaired fasting glucose was associated with all-cause mortality but not mildly raised HbA1c (39-47 mmol/mol)<sup>[33]</sup>. However, there are no studies that looked at the relationship between age of onset of Prediabetes and all-cause mortality, so more research is needed in this area to warrant further discussion. Intuitively if we manage to delay the onset of Prediabetes, we may be able to delay the onset of T2DM and there is strong evidence of the effectiveness of diabetes prevention programs<sup>[34-36]</sup>.

## CONCLUSION

In this narrative review, we found strong evidence of the relationship between age of onset of T2DM and all-cause mortality, good evidence of the relationship between age of onset of T1DM and all-cause mortality and no evidence of the relationship between age of onset of Gestational Diabetes or Prediabetes and all-cause mortality. Further research is needed to look at whether aggressive management of earlier onset of T2DM can help to reduce premature mortality.

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