Adverse Childhood Experiences (ACEs) and Diabetes | A brief review

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ADVERSE CHILDHOOD EXPERIENCES

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Adverse Childhood Experiences (ACEs) and Diabetes | A brief review

Karen Hughes, Kat Ford and Mark A Bellis

Introduction

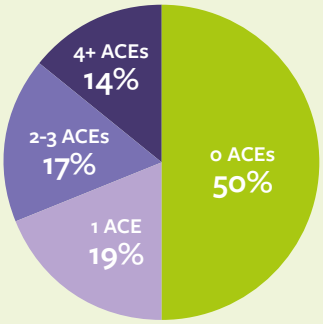
Children who suffer adverse childhood experiences (ACEs; see Box 1) are at increased risk of adopting health-harming behaviours and developing mental and physical illness across the life course.[1] The more ACEs children suffer, the greater their risks of developing poor health.[2-4] Diabetes is one of many health conditions that have been associated with ACEs. A review found that adults who had suffered four or more ACE types had a 52% greater risk of having diabetes than those who reported no ACEs.[1] However, most studies included in the review had not distinguished between diabetes types. The two main types of diabetes – type 1 and type 2 – share common characteristics yet are separate conditions with different development patterns (see Box 2). This document presents findings from a brief review undertaken to identify specific relationships between ACEs and type 1 and type 2 diabetes.

Box 1: What are ACEs?

ACEs are stressful events in childhood such as suffering abuse, neglect or living in a household affected by domestic violence or substance misuse. These kinds of experiences can be traumatic to children and can have harmful impacts on their neurological, physiological and social development; particularly if they are chronic and children do not have access to supportive relationships and other resilience resources.[4]

Half of adults in Wales report having suffered at least one ACE whilst growing up and 14% report having suffered four or more ACEs.[4,a]

Figure 1: Prevalence of ACEs[a] in the Welsh adult population



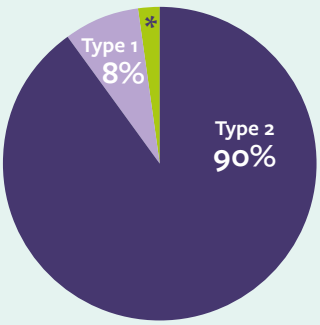
Box 2: What is diabetes?

Diabetes is a metabolic condition in which a person's blood glucose (sugar) level is too high due to their body being unable to produce or process insulin, the hormone which enables cells to absorb glucose from the bloodstream to use for energy. There are two main types of diabetes:

Type 1 diabetes is an autoimmune disease in which the body's immune system attacks and destroys the cells that produce insulin. It is usually diagnosed in childhood and its causes are still largely unknown, with both genetics and environmental factors playing a role.

Type 2 diabetes is a condition in which the body becomes resistant to insulin or does not produce enough of it. Type 2 diabetes is usually diagnosed in adulthood and is often related to lifestyle factors such as being overweight or physically inactive.

Figure 2: Distribution of diabetes types in the UK



*Other forms of diabetes 2%; see **www.diabetes.co.uk**

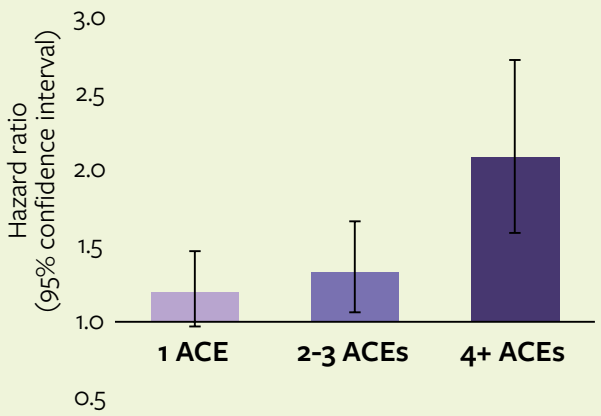
Almost 200,000 people in Wales are known to have diabetes and numbers are rising year on year. **Around 90% of adults with diabetes have type 2 diabetes.**[5]

[a] Data from the 2017 Welsh ACE and Resilience Study. ACEs measured included: physical abuse, verbal abuse, sexual abuse, physical neglect, emotional neglect, parental separation or divorce, exposure to domestic violence, and household member alcohol abuse, drug abuse, mental illness and incarceration.[4]

Methods

We conducted a rapid search in MEDLINE combining the keyword *diabetes* with terms including *adverse childhood experiences*, *childhood adversity, childhood trauma and child maltreatment*. We retrieved 247 references and accessed the full text of 132 relevant articles. Of these, 34 studies reported data on the risks of diabetes associated with ACEs. Searches were supplemented by screening the reference lists of relevant articles and conducting targeted searches to identify further studies on type 1 diabetes and childhood stressors, due to a lack of identified research using the ACE framework.

Figure 3: Hazard ratios for type 2 diabetes in UK ACE studies*



* Combined data from Ashton et al, 2016[3]; Bellis et al, 2013[8], 2015[6]; Ford et al, 2016[7]. Total sample 15,285 aged 18-69 years. Analysis controlled for study, gender, ethnicity and residential deprivation quintile.

Results

Number of ACEs and risk of diabetes

We identified 24 studies exploring relationships between the number of ACEs adults had suffered and diabetes. Of these, five had measured type 2 diabetes, two adult-onset diabetes, one diabetes medication reimbursements and the remainder had measured any diabetes without specifying type.

Type 2 diabetes

Four of the five studies measuring type 2 diabetes had been conducted in the UK. They included the Welsh ACE study[3] and three English ACE studies.[6-8]
All studies had used general adult population samples, asking participants if they had ever been diagnosed with type 2 diabetes.[b] The Welsh ACE study found that, compared with adults with no ACEs, those with 1-3 ACEs were twice as likely to have been diagnosed with type 2 diabetes and those with 4+ ACEs were four times as likely. Conversely, a study in North West England found no association between ACE count and type 2 diabetes, while the other two studies found increased risks in those with either 2-3[7] or 4+ ACEs.[6]

We combined data from the four UK studies and found that, compared with adults with no ACEs, those with 2-3 ACEs had a 1.3 times greater risk of type 2 diabetes and those with 4+ ACEs had a 2.1 times greater risk (Figure 3).

The remaining study had been conducted in a primary care sample in the USA. This found that risks[c] of patients having been diagnosed with type 2 diabetes increased with ACE count.[9]

Adult-onset diabetes

A UK study using the Whitehall II cohort explored the development of diabetes in later adulthood, measured through self-reported diagnosis, use of diabetes medication or biological measures. It found that each additional ACE was associated with an 11% increase in risk of diabetes. The relationship between ACEs and diabetes was mediated by cardiometabolic dysregulations and depression.[10] The other study in this category used World Mental Health Survey data from ten countries, asking participants if and when they had ever been diagnosed with diabetes or high blood sugar.[11] It found an increased risk[d] of diabetes in adults with 3+ ACEs (compared with those with none). With most adult-onset diabetes being type 2, the majority of participants with diabetes in both studies are likely to have had this type of diabetes.

Diabetes medication reimbursements

The only ACE study providing an indication of risk of type 1 diabetes was from Finland.[12] It linked self-reported data on ACEs and diabetes to official data on diabetes medication reimbursements, categorised as:

- insulin medication only (indicative of type 1)
- oral medication only (indicative of type 2)
- insulin and oral medication (indicative of type 2)
- self-reported diabetes but no medication (indicative of type 2 or misdiagnosis)

Compared with adults with 0-1 ACEs, those with 2-6 ACEs had an increased risk[e] of being in the combined insulin and oral medication group; suggested as potentially reflecting hard-to-manage type 2 diabetes. No association was found between ACEs and insulin medication only.

b Analyses in all studies accounted for age, gender, deprivation and ethnicity
c Controlling for age, gender and race
d Controlling for country, age and gender; inclusion of education level had no impact on results
e Controlling for age, sex, depression, body mass index and alcohol use

Unspecified diabetes

Most of the remaining 16 studies had asked adult participants a question such as *Have you ever been diagnosed with diabetes*? while some had used objective measures, such as fasting plasma glucose levels. All but four had been undertaken in the USA, where the distribution of diabetes is similar to that in the UK (around 90% of adults with diabetes have type 2[13]). Most found an increased risk of diabetes associated with ACEs.[f] For example, the US ACE study found an increased risk of diabetes in individuals with 4+ ACEs (compared to those with no ACEs), but no association in lower ACE categories.[14] A general population study using data from the US Behavioral Risk Factor Surveillance System (BRFSS) found a greater risk of diabetes at any level of ACEs,[15] while a different study using BRFSS data found that relationships between diabetes and ACEs were stronger in younger adults (aged <40 years).[16] Elsewhere, a study of older adults in Ireland found no association between diabetes and having 2+ ACEs (the highest ACE level analysed).[17] However, associations have been found between diabetes and ACEs in general population studies in Germany,[18] Saudi Arabia[19] and (when combined with living in a disadvantaged neighbourhood in adulthood) Finland.[20]

Individual ACE types and risk of diabetes

Various studies were identified that had measured relationships between specific ACE types and diabetes. As with studies on cumulative ACEs, these predominantly focused on unspecified or type 2 diabetes and on child maltreatment. A meta-analysis of such studies estimated that risks of type 2 diabetes were 1.3 times higher in adults that had suffered childhood physical abuse, 1.4 times higher in those that had suffered childhood sexual abuse, and 1.9 times higher in those that had suffered neglect.[21] Across the studies identified in our searches, several reported no independent associations between diabetes and parental substance use, death or mental illness.[11,15,22,23] Mixed findings were reported for relationships between diabetes and emotional abuse, domestic violence, parental separation or criminal behaviour in the family.[11,15,18,22,24]

Using the combined UK ACE data and a separate model for each individual ACE type, we found type 2 diabetes to be associated with physical abuse, verbal abuse and sexual abuse, domestic violence, and household mental illness and alcohol abuse, but not parental separation, household drug abuse or incarceration of a family member. However, in a model including all nine ACE types, independent relationships were only found with physical abuse and domestic violence (see Table 1).

Table 1: Hazard ratios for type 2 diabetes associated with individual ACEs in UK ACE studies*

	Models for individual ACEs	Model for all ACEs
ACE	**Hazard ratio**	**Hazard ratio**
Physical abuse	1.5	1.3
Verbal abuse	1.4	ns
Sexual abuse	1.4	ns
Domestic violence#	1.6	1.4
Mental illness#	1.4	ns
Alcohol abuse#	1.4	ns

*Combined data from Ashton et al, 2016[3]; Bellis et al, 2013,[8] 2015[6]; and Ford et al, 2016.[7] Total sample 15,285 aged 18-69 years. Analysis controlled for study, gender, ethnicity and deprivation quintile. #In household members. ns, not significant. No significant associations were found with parental separation, household drug abuse or incarceration of a family member.

Type 1 diabetes and early life stress

Further searches identified a body of research examining the impacts of early life stress on risks of type 1 diabetes. Whilst these studies had not used the ACE framework, the types of stressors they measured included ACEs such as parental violence and separation. Various studies found that children with type 1 diabetes had suffered more early life stress in the period prior to diagnosis than non-diabetic control children.[25,26] However, early reviews concluded that, as most studies were retrospective and small scale, there was a lack of robust evidence and a need for more refined study methodologies.[25,27]

More recently, several large prospective studies have increased support for the role of early childhood stress in type 1 diabetes development.[28] For example, a study following over 10,000 babies in Sweden found that those who were exposed to any of a range of serious life events (e.g. death of a relative, parental divorce, family conflict) had around a threefold increased risk[g] of later diagnosis of type 1 diabetes.[29] Another large prospective study in Sweden found that severe life events in a child's first two years of life were associated with a 1.7 times increased risk of later diagnosis of type 1 diabetes.[30]

f Studies typically controlled for at least some socio-demographic variables with several also incorporating health status variables into their models. See individual studies for details.

g Controlling for age, heredity for type 1 and type 2 diabetes, size for gestational age, parental education and parental employment prior to child's birth.

Do ACEs contribute to type 1 diabetes?

Although the precise causes of type 1 diabetes remain unknown, there is consensus that both genetic and environmental factors play a role.[31] Childhood stress – such as that imposed by ACEs – has long been proposed as a potential risk factor, yet robust evidence has been lacking. With the prevalence of type 1 diabetes increasing globally, there is renewed interest in the role of stress in the development of type 1 diabetes. The current ACE literature offers little evidence to either support or refute this role. Most ACE studies use retrospective surveys with adults to identify relationships between ACEs and disease. This approach is not well suited to the exploration of links with type 1 diabetes, which typically develops in childhood and represents only a small proportion of adult diabetes. Only one ACE study identified in our searches provided an indication of risk of type 1 diabetes and this showed no relationship between ACEs and the diabetes medication pattern representative of type 1.[12]

Beyond the ACE literature however, there is a body of work exploring relationships between early life stressors – including common ACEs – and later development of type 1 diabetes. This tends to show that children with type 1 diabetes have suffered more serious life events than non-diabetic children and that exposure to early life stress may increase risks of later diagnosis of type 1 diabetes.[25,28] The recent advent of large prospective studies is strengthening support for these links, with one study concluding that the increased risk of type 1 diabetes associated with serious life events was equivalent to those for other factors such as birthweight, enterovirus infection and infant nutrition; although heredity remained the most important factor predicting type 1 diabetes.[29] However, there remains a clear need for more research to explore the potential links between ACEs and type 1 diabetes.

While the potential pathways linking early life stress to the development of type 1 diabetes remain unclear, toxic stress can affect children's neurological and physiological development in ways conducive to increased risk of type 1 diabetes. While a detailed discussion of these pathways is beyond the scope of this document, proposed mechanisms include alterations in the hypothalamic-pituitary-adrenal (HPA) axis, impacts on the immune system and the development of insulin resistance.[28] In brief, the body reacts to stress by releasing hormones that trigger physiological responses such as increased blood pressure, muscle tension and blood sugar levels – giving the body a surge of energy to help it respond to danger (i.e. fight or flight). Frequent or prolonged activation of the stress response system in childhood can lead to dysregulation in the HPA axis,[32-33] which controls reactions to stress and regulates other processes including the immune system, digestion, energy use and emotions. It can lead to excess production of hormones including glucocorticoids (e.g. cortisol), which contribute to insulin resistance, as well as increased pro-inflammatory markers and immune system suppression, which can increase vulnerability to disease.[32,33] These types of biological mechanisms provide plausible pathways through which ACEs could trigger islet autoimmunity and diabetes type 1.

There are several other mechanisms linking ACEs and type 1 diabetes that should be considered. Children with type 1 diabetes who suffer ACEs can be at greater risk of poor outcomes due to reduced caregiver ability to manage their condition (e.g. through mental illness[34]). The wider impact of ACEs may also affect individuals' ability to self-manage diabetes and increase their risks of poor outcomes (e.g. through health-harming, mental illness and greater vulnerability to disease). Thus, ACEs have been associated with increased risks of suicide attempt and cardiovascular disease in adults with type 1 diabetes.[35,36]

Children with diabetes may also be at increased risk of ACEs. Having a child diagnosed with type 1 diabetes can be highly distressing for parents and may impact on their mental health. A review found that one in five parents of children with type 1 diabetes reported psychological distress (e.g. anxiety, depression, post-traumatic stress disorder; measured 1-4 years following diagnoses).[37] The stress of managing type 1 diabetes can also cause family conflict, including parent-child conflict – particularly in adolescence.[38] Evidence also shows that children with disabilities are at increased risk of abuse,[39] and this may extend to those with diabetes. A US study found that type 1 diabetes was the most common condition among paediatric patients reported to protective services for medical neglect.[40]

Do ACEs contribute to type 2 diabetes?

Available evidence from the ACE literature suggests that individuals who suffer ACEs can be at increased risk of type 2 diabetes. Although only a small number of ACE studies have specifically measured type 2 diabetes, most of these report associations with ACEs. The majority of ACE studies use broader measures of diabetes without specifying type. However, as most adults with diabetes have type 2, it is likely that most participants with diabetes in these studies have type 2. Again, these studies typically find associations with ACEs. While most ACE studies control for socio-demographic confounding in their analyses, the factors taken into account can vary widely and this may influence findings. Few ACE studies control for other childhood factors that may increase risk of type 2 diabetes, while several control for adult health outcomes that are also strongly related to ACEs (e.g. alcohol use, mental illness) and this may mask the extent of relationships between ACEs and diabetes. Thus, despite the general agreement in findings, there remains a need for more research to clarify pathways between ACEs and type 2 diabetes.

Systematic reviews[41,42] suggest that ACEs can impact on risks for type 2 diabetes both directly via their biological effects, and indirectly through their effects on mental health and health-harming behaviours. Thus, along with impacts on the HPA axis, insulin resistance and the immune system (see previous section), childhood trauma can have harmful impacts on neurological, social and emotional development. Individuals that suffer ACEs can have lower levels of self-esteem, trust, hope and self-efficacy and are at substantially increased risk of low mental wellbeing and mental illness, including anxiety, depression, eating disorders and suicide ideation, as well as post-traumatic stress disorder.[1,32,43] In turn, they are at increased risk of adopting health-harming behaviours such as smoking, heavy alcohol consumption, poor diet and physical inactivity.[1] All of these lifestyle behaviours can increase the risk of type 2 diabetes development.

Globally, the increasing prevalence of type 2 diabetes is widely acknowledged to be driven by increasing levels of obesity, sedentary lifestyles and unhealthy diets.[44] Systematic reviews have found increased risks of being overweight and obese associated with having multiple ACEs,[1] and with various forms of child maltreatment, including emotional abuse, physical abuse, physical neglect and sexual abuse.[45] In fact, the global ACE research framework emerged from work in a US obesity clinic which found a history of childhood sexual abuse in more than half of its patients, and identified over-eating to be a mechanism for coping with childhood trauma.[46]

Research has identified both obesity and depression to be key pathways linking sexual abuse to adult diabetes.[47] Equally, a UK study identified depressive symptoms and cardiometabolic dysregulations as pathways via which cumulative ACEs were linked to the development of diabetes in adulthood.[10] Cardio-metabolic dysregulations include markers such as central obesity, high blood pressure, high blood sugar levels, high triglyceride levels and abnormal cholesterol levels. The clustering of such markers is termed metabolic syndrome, and individuals with metabolic syndrome have three to five times greater risk of developing diabetes.[48] ACEs have been associated with a clustering of metabolic risk markers and metabolic syndrome.[49,50]

The combined effects of ACEs in embedding biological vulnerability to disease and promoting harmful lifestyle behaviours present a strong case for increased risk of type 2 diabetes among individuals that have suffered ACEs. They also mean that individuals with type 2 diabetes that have suffered ACEs can be vulnerable to poorer outcomes. Such individuals may have less self-efficacy in managing their condition and greater difficulty in making positive lifestyle changes, such as losing weight, increasing physical activity, reducing alcohol consumption and stopping smoking. A US study found that adults with smoking-exacerbated diseases (including diabetes, type unspecified) were more likely to continue smoking if they had ACEs.[51]

Accordingly, ACEs have been associated with poorer physical and mental health in adults with type 2 diabetes, whereas social connectedness and diabetes-related support have been found to moderate these effects.[52] While research exploring the impacts of ACEs on outcomes for individuals with type 2 diabetes is still in its infancy, there is a wealth of evidence showing that those with type 2 diabetes and poor mental health suffer poorer quality of life and worse outcomes than those with better mental health, including lower treatment compliance, increased risk behaviours such as smoking, poorer glycaemic control, and increased risks of cardiovascular disease and mortality.[53,54]

Summary

Whilst there is a relatively consistent body of evidence linking ACEs to type 2 diabetes, evidence linking ACEs to type 1 diabetes remains more limited. Although the ACE framework is suited to measuring relationships between ACEs and type 2 diabetes, the identification of such relationships with type 1 diabetes requires more refined, prospective studies. Recently, such studies have started to emerge, exposing associations between experiencing some types of serious life events and type 1 diabetes. Moreover, increasing evidence on the biological impacts of ACEs shows plausible pathways through which childhood trauma can affect risks of both types of diabetes. Equally, individuals with either type of diabetes that have suffered ACEs can be at greater risk of poor outcomes, raising issues for the consideration of ACEs in their management. An understanding of the childhood history of patients with diabetes may support the development of appropriate care pathways to facilitate management and improve outcomes for those affected by either type of diabetes.

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