# The Relationship Between Type 2 Diabetes Mellitus and the Development of Alzheimer's Disease

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Type 2 Diabetes Mellitus (T2DM) and Alzheimer's Disease (AD) are two prevalent and debilitating conditions with a surprising relationship. This research paper delves into the nuanced relationship between T2DM and AD, to elucidate the connection between these seemingly distinct disorders. Environmental and lifestyle influences, including ambulation, diet, noise, air pollution, and sleep patterns, significantly impact the risk of both T2DM and AD. These factors highlight the importance of modifiable lifestyle choices in disease prevention and intervention. Ethnicity and gender further shape susceptibility to T2DM and AD, with distinct genetic predispositions and hormonal influences contributing to differential risks among populations. Understanding these disparities is crucial for promoting health equity and tailored interventions. Genetic factors, such as the Apolipoprotein E (APOE) gene, Insulin Receptor Substrate 1 (IRS-1), Transcription Factor 7-Like 2 (TCF7L2), and signaling factors, elucidate shared pathways underlying T2DM and AD pathogenesis. Insights into these genes offer potential targets for therapeutic interventions. Moreover, insulin signaling pathways, including PI3K/AKT, mTOR, AMPK, GSK3$\beta$, JNK, and NF-$\kappa$B, reveal intricate molecular mechanisms linking T2DM and AD. Dysregulation of these pathways contributes to disease progression, emphasizing the need for targeted therapeutic strategies. Understanding the nuanced relationship between T2DM and AD provides crucial insights into disease etiology and therapeutic avenues. By integrating research across environmental, genetic, and molecular domains, novel disease prevention and management approaches can be developed, ultimately mitigating the global burden of T2DM and AD and nurturing a healthier future.

## Introduction

Despite their seemingly disparate manifestations - one primarily affecting metabolic homeostasis and the other targeting cognitive function - research has increasingly pointed towards shared underlying pathologic mechanisms involving metabolic signaling pathways and genetic risk factors that synergistically work to cause the combined diabetic-type dementia. T2DM, which is the most common type of diabetes in adults, characterized by insulin resistance and dysregulated glucose metabolism, has long been recognized as a major global health concern. Conversely, AD stands as the leading cause of dementia, robbing millions of their cognitive faculties and placing an immense strain on healthcare systems and societies.

This research paper explores the nuanced relationship between T2DM and AD, exploring the link between these seemingly distinct disorders. By synthesizing findings from various studies, we aim to comprehensively understand how T2DM influences the development and progression of AD pathology, and vice versa.

Key factors explored in this paper include environmental and lifestyle influences, genetic predispositions, ethnicity and gender, and the insulin signaling pathways involved in the two diseases to further understand the nuanced relationship between T2DM and AD.

Through this exploration, we endeavor to deepen our understanding of the convoluted interactions between T2DM and AD and pave the way for novel strategies to mitigate the burden of both diseases. Ultimately, understanding the nuanced relationship between T2DM and AD holds the promise of advancing personalized medicine approaches and improving outcomes for individuals affected by these debilitating conditions.

## Methods

This research paper focused on the specific etiologies (environmental and lifestyle factors, ethnicity and gender, genetics, and insulin signaling pathways) in the relationship between T2DM and AD that encompassed the most influential and diverse aspects of disease risk and progression and provided a comprehensive framework for understanding the interplay between T2DM and AD. The research paper is organized based on these etiologies. Important factors were researched for each section and categorized based on those factors. Quantitative research in the literature was reviewed to collect statistics about these factors and then compared these statistics to draw conclusions about the relationship between T2DM and AD. The initial screening was performed using Google and the search terms

"dementia", "Alzheimer's", and "diabetes", and used PubMed to yield more than 150 relevant research papers that had these combinations of terms and researched specific factors and their influence on the relationship between T2DM and AD. However, if the research paper only talked about one of the two diseases, those papers were put aside and used only if there wasn't enough research present about the factor's influence on both diseases. This produced a final yield of 70 papers meeting the above criteria.

### Limitations

This literature review encompasses a broad range of studies exploring the relationship between Type 2 Diabetes Mellitus (T2DM) and Alzheimer's Disease (AD). However, several limitations inherent in these studies should be considered. One significant limitation is the sample size and generalizability of some studies. For instance, the study on the impact of air pollution on T2DM and AD risk, which found that air pollution increases the risk of T2DM by 19% and 40% and the odds risk for AD by 1.00 and 0.95 with respective p-values of 0.004 and 0.165, had a sample size of only 200 participants from a single city, limiting the generalizability of the findings to other populations with different environmental exposures or genetic backgrounds. Another limitation is the potential for p-hacking and statistical issues. In the study examining physical activity's impact on reducing the risk of AD by 45% (p=0.006) and T2DM by 19% (p=0.004), there are concerns about potential p-hacking as the researchers reported multiple subgroup analyses without appropriate corrections for multiple comparisons, affecting the reliability of the conclusions drawn. Additionally, underlying assumptions in some studies can limit their validity. A study on the role of the APOE gene in T2DM and AD that says that an increase in APOE $\varepsilon 4$ leads to a 1.5 times higher risk of T2DM (p=0.04) assumes that the presence of the APOE $\varepsilon 4$ allele is uniformly detrimental across all ethnic groups, although its impact can vary significantly due to genetic and environmental interactions, affecting the study's conclusions about the general role of APOE $\varepsilon 4$ in disease risk. The failure to adequately control for confounding variables is another limitation. The studies investigating the effect of diet on T2DM and AD risk, which reported that consumption of saturated and trans fats increases the incidence of T2DM by 23% (p=0.03) and the risk of AD by 2 to 3 times (p=0.03), did not control for confounding variables such as socioeconomic status, physical activity levels, and other lifestyle factors, making it challenging to isolate the impact of diet alone on disease outcomes. Bias in self-reported data also poses a limitation, as several studies relied on self-reported data for lifestyle factors such as diet, physical activity, and sleep patterns, which are prone to recall bias and social desirability bias, potentially skewing the results and leading to inaccurate associations between lifestyle factors and disease risk. Lastly, ethnic and gender representation in some studies is limited. Many of the studies are based on comparisons between the Caucasian populations with other ethnic groups such as African American, Asian American, and Hispanic groups, limiting the applicability of findings to other ethnic groups. For instance, the studies on genetic predispositions for T2DM and AD mention genes like APOE, IRS-1, and TCF7L2 but may not accurately reflect risks in African American or Hispanic populations who have different genetic and environmental risk factors. The more modern technology of higher dimensional multi-omic studies including proteomics and genomics may better elucidate the mechanisms underlying the connection between T2DM and AD. By critically evaluating these aspects of the sources, we can better understand the limitations of the existing literature and identify areas where further research is needed to strengthen the evidence base on the relationship between T2DM and AD.

## Discussion

### Environmental and Lifestyle Factors

Multiple environmental and lifestyle factors are involved in the relationship between T2DM and the formation of AD, including, but not limited to, walkability, diet, green space, noise, pollution, and sleep (see Table 1). Walkability, the ease with which an area supports walking, has been linked to a lower risk of T2DM, as people in areas with higher walkability have been found to have a 12% lower chance of getting T2DM[1]. Physical activity, in general, has been found to reduce the risk of T2DM by 19% and the risk of AD by 45%[1,2]. As physical activity decreases the impact of common etiologies of T2DM and AD such as hypertension (by 5-7 mmHg) and dyslipidemia (by decreasing the total:HDL cholesterol ratio from 3.41 to 2.92 when people exercised 150 minutes weekly)[3,4], physical activity has an enormous impact on the relationship between T2DM and AD and the factors known to link them together.

Diet is another factor that has been found to impact the relationship between T2DM and AD. Individuals with greater access to healthy food options have a 37% lower risk of developing T2DM compared to those with limited access[1]. Carbohydrate intake increases the cerebral load of $\beta$-amyloid, the aggregation of which is associated with AD in 26% of healthy older adults[5]. The consumption of food containing saturated and trans fats is a common factor between T2DM and AD as it is pro-inflammatory, increasing the incidence of T2DM by 23% in Swedish men and women and increasing the risk of AD 2 to 3 times[6,7]. Calcium and vitamin D are known protective factors against T2DM and AD. The consumption of calcium and vitamin D reduces the risk of T2DM and AD, decreasing the risk of T2DM by 33%[8]. Deficiency of Vitamin D increases the risk of AD by 51% and, if severely deficient, by 122%[9]. Multiple studies show that diet is a significant factor in the synergistic

relationship between T2DM and AD.

Furthermore, noise is another factor that has been found to impact the relationship between T2DM and AD. An increase of 10 dB of road traffic noise at current residence has been found to increase the incidence of T2DM by 8%[1] and 30% for AD[10]. Noise has been found to exacerbate common factors of T2DM and AD such as stress, which was measured through an ICD-10 diagnostic. Minimal perceived stress accounts for 10% of T2DM risk, moderate/high perceived stress accounts for 20% of T2DM risk, and chronic stress/depression accounts for an increase in the odds ratio for AD by 3.55[11,12]. Additionally, noise can increase irregular sleep patterns, which increase the number of amyloid plaques. Difficulty initiating sleep increases the risk of T2DM by 55%, difficulty maintaining sleep increases the risk of T2DM by 74%, and irregular sleep leads to a 53% increased risk of dementia[13,14]. Given these findings, noise has been established as a huge factor in the relationship between T2DM and AD.

Additionally, air pollution is another factor that has been found to impact the relationship between T2DM and AD significantly. A 10 g/m[1] increase in $NO_2$ and $PM_{10}$ leads to the chances of contracting T2DM increasing by 19% and 40% respectively1 and the odds risk for AD increasing by 1.00 and 0.95 respectively[15]. Along with this, pesticides have been linked with a 60% increased risk of getting T2DM and the risk of getting AD quadrupling[16]. Air pollution has been found to exacerbate common factors of T2DM and AD. These common factors include systemic inflammation. Chronic inflammatory disorders increase the risk of T2DM by 20%[16]. They also increase the 10-year risk of developing AD by 1.12% (if rheumatoid arthritis is present) and 1.09% (if multiple sclerosis is present)[17]. Another common target exacerbated by air pollution is endothelial dysfunction. Microcirculatory dysfunction increases the risk of getting T2DM by 71%[18]. Vascular pathology has been found in 80% of AD patients[19]. Therefore, air pollution is an enormous factor in the relationship between T2DM and AD.

Finally, sleep is another factor that has been found to impact the relationship between T2DM and AD. T2DM was linked to nearly regular reports of trouble falling asleep (21.1%), trouble staying asleep (21.9%), and excessive daytime sleepiness (12.2%)[20] and sleep disturbance has been found to increase the risk of developing AD by 51%[21]. A lack of sleep has been found to exacerbate common factors of T2DM and AD such as obesity and inflammation. Obese people have a risk of getting T2DM that is seven times higher than that of people without obesity[22] and are at an 80% increased risk of getting AD[23], while increased prevalence of inflammatory markers such as interleukin-6 (IL-6) and C-reactive protein (CRP) have been found in T2DM[24] and AD[25].

In conclusion, the multifaceted relationship between T2DM and AD underscores the interactions of environmental and lifestyle factors in shaping disease risk and progression. Factors such as walkability, diet, noise, air pollution, and sleep have emerged as significant determinants that influence individual susceptibility to T2DM and AD and serve as potential avenues for intervention and prevention. Encouragingly, modifiable lifestyle factors, including physical activity, dietary habits, and sleep hygiene, offer promising opportunities to mitigate the risk of both T2DM and AD. However, comprehensive strategies addressing the interactions between these factors are crucial for developing effective preventive measures and therapeutic interventions to combat the rising burden of T2DM and AD on a global scale. By prioritizing research, public health initiatives, and individual lifestyle modifications, we can strive towards a future where the impact of T2DM and AD is minimized, promoting optimal health and well-being for all.

**Ethnicity and Gender**

Studies also show that an important factor in the relationship between T2DM and AD is ethnicity, which is based on geography when it comes to the relationship between T2DM and the development of AD. Different ethnicities tend to have different genetic predispositions that may increase or decrease their chances of getting T2DM and AD (see Table 2). For example, compared to Caucasians, Hispanic people have a 5% higher chance of getting T2DM[26]. They are also 1.5 times more likely to get AD[27]. African Americans have a 60% higher chance of getting T2DM[28] and are 2 times more likely to get AD[27]. For Hispanic people, the reasoning for this is that they tend to have more staple foods, such as tortillas, rice, and beans, which can cause spikes in blood sugar levels and obesity (symptoms of T2DM), in their diet[29]. They suffer from lower access to healthcare than the general population due to many reasons, including language proficiency, immigration status, socioeconomic status, and level of acculturation[29]. All of this, in turn, leads to them having higher chances of getting AD[30]. For African Americans, the reasoning for this is that they tend to have greater body masses and have more abdominal obesity (symptoms of T2DM) than Caucasians and tend to have more agitation/aggression, loss of inhibition, irritability, motor disturbances, abnormal sleep, and behavioral and appetite/eating changes (symptoms of AD) than Caucasians[31]. Along with this, African Americans tend to seek medical treatment when they encounter neuropsychiatric symptoms such as hallucinations, delusions, and personality changes, but delay help for memory problems, as they are often viewed as a normal part of aging[31]. For Asian Americans, however, the story is a bit different; they are 40% more likely to be diagnosed with T2DM than Caucasians[32] but are 2% less likely to get AD than Caucasians[33]. The reason for this is that Asian Americans tend to have less muscle but more fat (a risk factor for T2DM)[34] than Caucasians but tend to have lower levels of Apolipoprotein E (APOE) $\varepsilon 4$[35], which is a key gene for the formation of AD that will be discussed in the next section of

| Factor | T2DM | AD |
|---|---|---|
| Obesity | x7 (95% CI, 5.74 to 9.00) | 80% (95% CI, 1.00 to 3.29) |
| Pesticides | 60% (95% CI, 1.32 to 1.90) | x4 (95% CI, 2.54 to 5.82) |
| Saturated and Trans Fats | 23% (p=0.03) | x2-3 (p=0.03) |
| Physical Activity | -19% (95% CI, 0.71 to 0.88) | -45% (p=0.006) |
| Noise | 8% (95% CI, 1.02 to 1.14) | 30% (95% CI, 1.08 to 1.55) |

**Table 1** Summary of Environmental and Lifestyle Factors and Impact on Change in Risk of T2DM and AD

this review. Along with this, Asian Americans are much better at recognizing signs of AD and know more about it than other ethnicities[35].

Another important factor in the relationship between T2DM and AD is gender. Being a male or a female can lead to being more or less prone to getting T2DM and AD. Men are two times more likely to get T2DM than women[36] but they are two times less likely to get AD than women[37]. The main reason for this is the sex hormones in men and women. Women have more of the sex hormone estrogen, which stimulates cells that line blood vessels to deliver insulin to muscles, lowering blood sugar and protecting against T2DM[38] but exposes them to an increased risk of AD during menopause as the protective effect of estrogen against AD is decreased with the decreased amount of estrogen[37]. Men, on the other hand, have a higher amount of testosterone, which protects against AD through androgen receptors[39]. As a result of this, compared to women, men are more likely to get T2DM due to having less estrogen but are less likely to get AD as they have lower amounts of estrogen, don't go through menopause, and have higher amounts of testosterone. Analyzing the impact of gender and sex hormones on the relationship between T2DM and AD will become increasingly important in the future with the increasing prevalence of both diseases.

The relationship between T2DM and AD is profoundly influenced by ethnicity and gender, reflecting the elaborate connections between genetic predispositions, lifestyle factors, and hormonal influences. Ethnic disparities in T2DM and AD prevalence underscore these conditions, with Hispanic and African American populations exhibiting heightened risks due to genetic susceptibilities and dietary habits. Conversely, Asian Americans demonstrate unique trends, highlighting the importance of ethnicity-specific considerations in disease management. Moreover, the gender-specific differences in T2DM and AD susceptibility shed light on the role of sex hormones, with estrogen protecting against T2DM but potentially increasing the risk of AD in women, while testosterone may confer protection against AD in men. Understanding these ethnic and gender disparities is crucial for developing targeted interventions and promoting health equity. Moving forward, continued research into the underlying mechanisms driving these relationships will be essential for developing personalized approaches to disease prevention and management, ultimately improving outcomes for individuals affected by T2DM and AD across diverse populations.

## Genetics

Along with environmental, lifestyle, ethnic, and gender factors, numerous genes appear to be involved in the relationship between T2DM and the formation of AD. This review, however, will go over some of the most significant ones. All of the following genes have been identified as significant in the relationship between T2DM and the formation of AD due to their prevalence and strength in genome-wide association studies (GWAS).

APOE is one of the most well-established genetic risk factors for late onset AD[40], with the E4 isoform encoded by the $\varepsilon 4$ allele associated with increased AD risk and T2DM risk (see Fig. 1). A GWAS study identified it as the strongest genetic risk factor in the relationship between T2DM and AD[41] (see Table 3). One copy of APOE $\varepsilon 4$ is associated with a threefold increase in AD risk[41] (see Fig. 2, 3) and although there was a 1.5-fold increase in T2DM risk (p=0.41), this was not statistically significant[42]. Having two copies of APOE $\varepsilon 4$ has been associated with a 10-fold increased risk of AD[41] (see Fig. 2, 3).

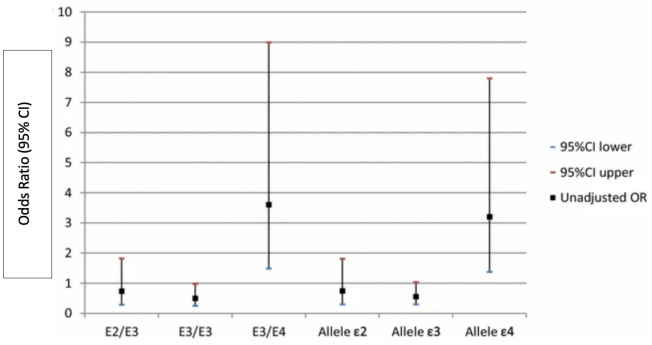


**Fig. 1** Association of APOE gene polymorphism with the risk of T2DM. Seen in a meta-analysis of GWAS studies. As the E4 isoform and $\varepsilon 4$ allele have a higher confidence interval, this shows how their presence is associated with a higher risk of T2DM[42] (forest plot).

APOE $\varepsilon 4$ causes synaptic loss around plaques in AD[41] and interacts with insulin receptors to impair their trafficking by trapping them in endosomes, leading to impaired insulin signaling and insulin resistance, a common mechanism of T2DM[44].

| Ethnicity | T2DM | AD |
|---|---|---|
| Hispanic | 1.05x | 1.50x |
| African Americans | 1.60x | 2.00x |
| Asian Americans | 1.40x | 0.98x |

**Table 2** Ethnicity and Impact on Risk of T2DM and AD Compared to Caucasians

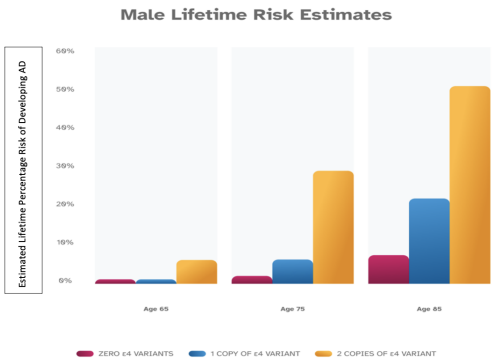


**Fig. 2** Male Lifetime Risk Estimates for AD due to Amount of $\varepsilon 4$ Alleles. Seen in an epidemiological study. As an increased amount of $\varepsilon 4$ alleles leads to an increased risk for AD, a positive correlation between the two can be seen[43]

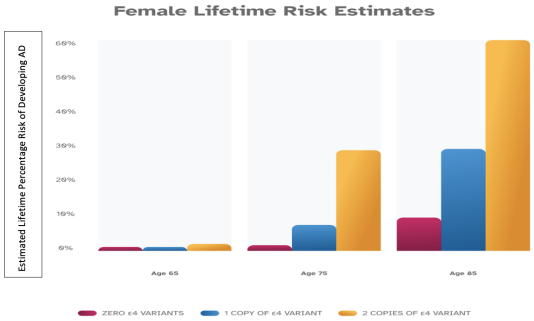


**Fig. 3** Female Lifetime Risk Estimates for AD due to Amount of $\varepsilon 4$ Alleles. Seen in an epidemiological study. As an increased amount of $\varepsilon 4$ alleles leads to an increased risk for AD, a positive correlation between the two can be seen[43]. At age 65, males are at a higher risk for AD, but at age 75 the risk for both males and females is relatively similar and at age 85 females are at a significantly higher risk (comparing Fig. 2 to Fig. 3).

However, the $\varepsilon 2$ variant of APOE has been found to increase the risk of T2DM twofold[45] while decreasing the chances of getting AD by 66% compared to those with the APOE2/3 genotype, 87% compared to those with the APOE3/3 genotype, and 99.6% compared to those with APOE4/4 genotype[46]. Due to its significant and varying impacts on AD and T2DM, APOE is crucial to the relationship between the two diseases and should be investigated more.

| | T2DM | AD |
|---|---|---|
| **APOE $\varepsilon 4$** | 1.50x (p=0.41) | 3.00x (95% CI, 2.03 to 3.96) |
| **APOE $\varepsilon 2$** | 2.00x (p=0.03) | 0.34x (95% CI: 98.6 to 99.9) |

**Table 3** Summary of APOE alleles and their impact on the risk of Type 2 Diabetes Mellitus (T2DM) and Alzheimer's Disease (AD).

Another important gene in the relationship between AD and T2DM is insulin receptor substrate 1 (IRS-1), a downstream effector of insulin signaling. IRS-1 has been characterized as causing disturbances in the relationship between T2DM and AD through GWAS studies[47]. IRS-1's major-C allele has been associated with a 19% increase in the risk of T2DM[48], and activated forms of ISR-1 such as IRS-1 $pY^{6}12$ and IRS-1 $pY^{9}41$ have a 162% and 73% increase in the risk of AD respectively[49]. IRS-1 causes increased fasting- and glucose-stimulated hyperinsulinemia and impaired insulin sensitivity in T2DM[48] and insulin resistance in the cerebellar cortex in AD[49]. Thus, IRS-1 is an important gene in the relationship between AD and T2DM due to its effects on the risks and pathology of both diseases.

Another gene that plays a role in the relationship between AD and T2DM is transcription factor 7-like-2 (TCF7L2), a gene located on chromosome 10q25 that acts as a transcription factor. The correlation between TCF7L2 and the relationship between T2DM and AD has been confirmed through GWAS studies[50] (see Fig. 4). TCF7L2 has been found to increase the risk of T2DM by 30-50% per allele inherited[51] and has been found to have 1.5 to 2 times the amount of messenger RNA (mRNA) present in people with AD than people without AD[52].

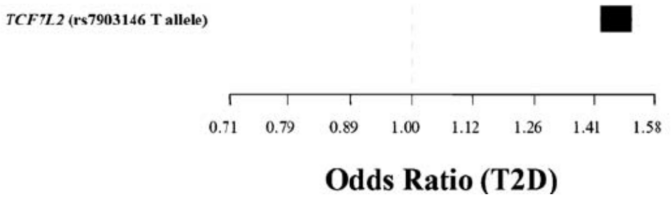


**Fig. 4** TCF7L2, the most reproducible risk for T2D by a gene variant so far: data shown is for allelic odds ratios based on meta-analyses previously published. The 95% CI for the meta-analysis is represented by a horizontal line. The square's area is proportional to the statistical weight of the meta-analysis. As seen, the odds ratio of T2DM increases with the presence of TCF7L2[53].

TCF7L2 has been found to play a role in adipogenesis, myo-

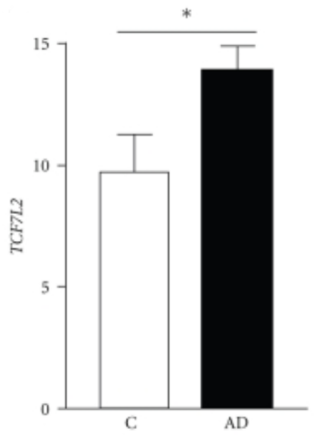


**Fig. 5** Relative mRNA levels of TCF7L2 in control (C) (n = 9) and AD (n = 13) brain as measured by quantitative PCR (qPCR), normalized to *glyceraldehyde 3-phosphate dehydrogenase* (GAPDH) and a calibrator sample (mean ± SEM, P ¡ .05 for both). The AD subjects have significantly higher levels of TCF7L2[52].

genesis, pancreatic islet development, beta-cell survival, and insulin secretory granule function[54], all of which contribute to T2DM. It has also been found to increase the progression from mild cognitive impairment (MCI) into AD[55] (see Fig. 5). Thus, TCF7L2 is another important gene in the relationship between AD and T2DM due to its effects on both diseases.

In conclusion, the relationship between T2DM and AD is influenced by a myriad of genetic factors that interact with environmental and lifestyle elements to shape disease susceptibility and progression. Among the key genetic factors discussed in this review, Apolipoprotein E (APOE) is a significant contributor to AD and T2DM risk, with its $\varepsilon 4$ allele associated with heightened susceptibility to both conditions. Notably, APOE $\varepsilon 4$ exacerbates synaptic loss in AD and impairs insulin signaling in T2DM, underscoring its pivotal role in the pathogenesis of both diseases. Similarly, insulin receptor substrate 1 (IRS-1) emerges as a crucial gene in the AD-T2DM relationship, with its major-C allele predisposing individuals to T2DM while also contributing to insulin resistance in AD. Additionally, transcription factor 7-like-2 (TCF7L2) influences the risk of T2DM and AD through its effects on adipogenesis, beta-cell function, and cognitive decline, highlighting its multifaceted role in disease pathogenesis. These genetic factors provide insights into the shared mechanisms underlying AD and T2DM and offer potential targets for therapeutic interventions to mitigate the burden of both diseases. While genetic studies have shown the importance of APOE, IRS-1, and TCF7L2 in the development of diabetes-AD dementia, it is clear that multiple genes are involved in this polygenic interaction, producing this complex syndrome. We have focused on a few select genes that have a potent effect on this interaction.

## Insulin Signaling Pathways

The last section of this paper will address the insulin signaling pathways that are correlated with the relationship between T2DM and AD. The effects of these insulin signaling pathways are not well understood because this area of research is a recent development in the relationship between T2DM and AD.

The first insulin signaling pathway to be addressed is the phosphoinositide-3-kinase-protein kinase B/Akt (PI3K/AKT) insulin signaling pathway. The PI3K/AKT insulin signaling pathway regulates cell proliferation, differentiation, metabolism, and cytoskeletal reorganization[56]. Under normal conditions, insulin activates the PI3K/AKT insulin signaling pathway, which increases glucose utilization, increases body lipid deposition thus increasing insulin production in the pancreas, regulating lipid and glucose metabolism balance, and reduces appetite in the brain[57]. However, in T2DM, lipids accumulate in skeletal muscles and cause the reduction of glucose transport and glycogen synthesis, leading to glucose metabolism imbalance[58]. All of those would impair the PI3K/AKT insulin signaling pathway, causing insulin resistance and eventually T2DM[59]. A decrease in activity of the PI3K/AKT insulin signaling pathway has also been noted in AD; this leads to a decrease of insulin in the brain which in turn explains the downregulation of O-GlcNAcylation and consequent hyperphosphorylation of tau and why tau molecules tend to aggregate together[60]. Thus, researching the PI3K/AKT insulin signaling pathway and its relation to the relationship between T2DM and AD will become extremely important in the future with the increasing prevalence of both diseases.

The second insulin signaling pathway to be addressed is the mammalian target of rapamycin (mTOR) insulin signaling pathway. The mTOR insulin signaling pathway uses nutrients to regulate cellular metabolism, growth, and survival[56]. However, a surplus of nutrients has been found to overstimulate the mTOR insulin signaling pathway and result in insulin resistance[61], a hallmark of T2DM, and amylin aggregation[62], a hallmark of AD. Therefore, investigating the role of the mTOR insulin signaling pathway in the interplay between T2DM and AD will be of paramount significance as the prevalence of both conditions continues to rise.

The third insulin signaling pathway to be addressed is the AMP-activated protein kinase (AMPK) insulin signaling pathway. The AMPK insulin signaling pathway regulates cellular energy balance and glucose homeostasis[63]. An increase in the activity of the AMPK insulin signaling pathway has been found to inhibit insulin resistance and reduce tau hyperphosphorylation and aggregation, revealing how stimulating the AMPK insulin signaling pathway in T2DM and AD patients can serve as a treatment. However, an increase in the activity of the AMPK insulin signaling pathway has been found to increase the aggregation of beta-amyloid, a common etiology of AD[64]. Hence, investigat-

ing the significance of the AMPK insulin signaling pathway in the interaction between T2DM and AD will be critically important given the escalating prevalence of these disorders and how the AMPK insulin signaling pathway has positive and negative effects on T2DM and AD patients.

The fourth insulin signaling pathway to be addressed is the glycogen synthase kinase 3 beta (GSK3$\beta$) insulin signaling pathway. The GSK3$\beta$ insulin signaling pathway contributes to insulin production to start glycogen synthesis. An increase in the activity of the GSK3$\beta$ insulin signaling pathway has been found to affect T2DM by increasing insulin resistance[65] and affect AD by increasing amyloid beta aggregation and tau hyperphosphorylation[66]. Therefore, exploring the importance of the increase of GSK3$\beta$ insulin signaling pathway activity in the interplay between T2DM and AD will become crucial in light of the increasing prevalence of these conditions.

The fifth insulin signaling pathway to be addressed is the c-Jun N-terminal kinase (JNK) insulin signaling pathway. The JNK insulin signaling pathway regulates metabolism. A decrease in the activity of the JNK insulin signaling pathway has been associated with a decrease in insulin resistance[62] and a decrease in the formation of plaques[67], revealing that a reduction in JNK insulin signaling pathway activity is associated with improvement in patients with one of or both diseases. Thus, investigating the significance of decreased JNK insulin signaling pathway activity in the interaction between T2DM and AD will be vital given the growing prevalence of these disorders.

The sixth insulin signaling pathway to be addressed is the nuclear factor-kappa B (NF-$\kappa$B) insulin signaling pathway. The NF-$\kappa$B insulin signaling pathway mediates inflammation and oxidative stress responses. An increase in the activity of the NF-$\kappa$B insulin signaling pathway has been associated with an increase in insulin resistance[68] along with $\beta$-site amyloid precursor protein (APP) cleaving enzyme-1 (BACE1)[69], symptoms of T2DM and AD respectively. Therefore, examining the importance of increased NF-$\kappa$B insulin signaling pathway activity in the interplay between T2DM and AD will be essential given the increasing prevalence of these conditions.

In conclusion, the insulin signaling pathways represent intricate molecular mechanisms underlying the nuanced relationship between T2DM and AD. While these pathways play pivotal roles in regulating cellular metabolism, growth, and survival, their dysregulation is associated with the development and progression of both diseases. The phosphoinositide-3-kinase–protein kinase B/Akt (PI3K/AKT) pathway, mammalian target of rapamycin (mTOR) pathway, AMP-activated protein kinase (AMPK) pathway, glycogen synthase kinase 3 beta (GSK3$\beta$) pathway, c-Jun N-terminal kinase (JNK) pathway, and nuclear factor-kappa B (NF-$\kappa$B) pathway each contribute uniquely to the pathogenesis of T2DM and AD. While some pathways exhibit dual effects, others demonstrate disparate impacts on the two conditions. Understanding the balance between these pathways is critical for understanding the dynamics of the combination of T2DM and AD. Moreover, elucidating the role of these pathways may pave the way for novel therapeutic strategies targeting shared molecular pathways, ultimately offering hope for improved management and treatment of both T2DM and AD amid their increasing prevalence in the population.

## Conclusion

The relationship between Type 2 Diabetes Mellitus (T2DM) and Alzheimer's Disease (AD) is influenced by a range of environmental, genetic, and lifestyle factors (see Table 4) that people could incorporate into their daily lives to reduce their risk of T2DM and AD. The literature review highlights significant associations between these diseases, yet several limitations in the existing research underscore the need for more rigorous and comprehensive studies.

One major gap is the generalizability of findings due to small sample sizes and limited population diversity. Future research should aim to include larger, more diverse cohorts to enhance the applicability of results across different populations and environmental contexts. For example, studies should consider varying genetic backgrounds and environmental exposures to provide a more holistic understanding of the T2DM and AD relationship.

Potential p-hacking and statistical issues, such as those identified in studies on physical activity's impact on AD and T2DM risk, highlight the need for stricter methodological rigor. Future studies should apply appropriate statistical corrections and ensure transparency in reporting all conducted analyses to avoid false-positive results.

The underpinning assumptions, like those seen in studies that focus on the APOE $\varepsilon$4 allele, must be critically examined and adjusted for population-specific differences. Research should explore how genetic factors interact with environmental and lifestyle factors across diverse ethnic groups to better understand their collective impact on T2DM and AD.

Addressing confounding variables is another crucial area for improvement. Studies on the effect of diet on T2DM and AD risk should better control for factors such as socioeconomic status, physical activity levels, and other lifestyle variables to isolate the true impact of dietary habits on disease outcomes. More comprehensive data collection and advanced statistical techniques can help achieve this.

The reliance on self-reported data introduces bias and inaccuracies, suggesting a need for more objective measures of lifestyle factors. Future research should incorporate wearable technology, biomarkers, and other objective data collection methods to reduce bias and improve data accuracy.

Lastly, ethnic and gender representation in current research could be more inclusive, limiting the generalizability of findings. Future studies should strive for more inclusive sampling

**Table 4** Summary of Major Etiologies and Impact on Risk of T2DM and AD

| | T2DM | AD |
|---|---|---|
| **Lifestyle** | | |
| Physical Activity | -19% | -45% |
| Saturated and Trans Fats | 23% | x2-3 |
| Obesity | x7 | 80% |
| **Environmental** | | |
| Noise | 8% | 30% |
| Pesticides | 60% | x4 |
| **Ethnicity** | | |
| Hispanic (Compared to Caucasians) | 5% | x1.5 |
| African Americans (Compared to Caucasians) | 60% | x2 |
| Asian Americans (Compared to Caucasians) | 40% | -2% |
| **Genetic** | | |
| APOE $\varepsilon 4$ | x1.5 | x3 |
| APOE $\varepsilon 2$ | x2 | -66% |

** This table combines data from previously presented tables*

strategies to ensure that findings are relevant to diverse populations. This includes focusing on underrepresented groups to identify unique risk factors and protective factors pertinent to those populations.

In summary, physical activity has a moderate effect on reducing the chance of T2DM by 19% and AD by 45%. Saturated and trans fats can increase the risk of T2DM by 23% and AD by x2-3. Obesity can increase the risk of T2DM by x7 and AD by 80%. Noise can increase the risk of T2DM by 8% and AD by 30%. Pesticides can increase the risk of T2DM by 60% and AD by x4. Compared to Caucasians, Hispanics have a higher risk of T2DM by 5% and AD by x1.5, African Americans have a higher risk of T2DM by 60% and AD by x2, and Asian Americans have a higher risk of T2DM by 40% and a decreased risk of AD by x2. Having APOE $\varepsilon 4$ increases the risk of T2DM by x1.5 and AD by x3, and APOE $\varepsilon 2$ increases the risk of T2DM by 2% and decreases the risk of AD by 66%. Recent biomedical research has shown that insulin signaling pathways PI3K/AKT, mTOR, AMPK, GSK3$\beta$, JNK, and NF-$\kappa$B have shown to play a key role in the progression of T2DM and AD and provide potential targets for drug development.By addressing these gaps, future research can provide more robust and actionable insights into the relationship between T2DM and AD, ultimately guiding better prevention and intervention strategies for these interconnected diseases.

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