



REVIEW ARTICLE

Does breastfeeding influence the risk of developing diabetes mellitus in children? A review of current evidence[☆]

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Abstract

Objective: the aim of this study was to perform a review to investigate the influence of breastfeeding as a protective agent against the onset of diabetes in children.

Sources: non-systematic review of SciELO, LILACS, MEDLINE, Scopus, and VHL databases, and selection of the 52 most relevant studies. A total of 21 articles, specifically on the topic, were analyzed (nine related to type 1 diabetes and 12 to type 2 diabetes).

Data synthesis: the duration and exclusivity of breastfeeding, as well as the early use of cow's milk, have been shown to be important risk factors for developing diabetes. It is believed that human milk contains substances that promote the maturation of the immune system, which protect against the onset of type 1 diabetes. Moreover, human milk has bioactive substances that promote satiety and energy balance, preventing excess weight gain during childhood, thus protecting against the development of type 2 diabetes. Although the above mentioned benefits have not been observed by some researchers, inaccuracies on dietary habit reports during childhood and the presence of interfering factors have been considered responsible for the lack of identification of beneficial effects.

Conclusion: given the scientific evidence indicated in most published studies, it is believed that the lack of breastfeeding can be a modifiable risk factor for both type 1 and type 2 diabetes. Strategies aiming at the promotion and support of breastfeeding should be used by trained healthcare professionals in order to prevent the onset of diabetes.

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O aleitamento materno influencia o risco de desenvolvimento de diabetes mellitus na criança? Uma análise das evidências atuais

Resumo

Objetivo: realizar uma análise crítica da literatura para avaliar a influência da amamentação no risco de desenvolvimento de diabetes *mellitus*.

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Diabetes mellitus tipo 2

Fonte dos dados: revisão não sistemática nas bases de dados SciELO, LILACS, MEDLINE, Scopus e BVS, selecionando-se 52 referências mais relevantes. Especificamente sobre o tema, foram analisadas 21 (sendo 9 para diabetes tipo 1 e 12 para diabetes tipo 2).

Síntese dos dados: a duração, a exclusividade do aleitamento materno e uso precoce do leite de vaca têm sido apresentados como fatores de risco para o desenvolvimento de diabetes. Acredita-se que o leite humano contenha substâncias que promovem a maturação do sistema imunológico protegendo contra o diabetes tipo 1. Além disso, ele possui substâncias bioativas, que promovem o equilíbrio energético e a saciedade, prevenindo o ganho de peso excessivo da criança e protegendo, conseqüentemente, contra o aparecimento do diabetes tipo 2. Apesar dos benefícios anteriormente citados não terem sido constatados por alguns pesquisadores, a imprecisão no relato dos hábitos dietéticos da infância e a presença de fatores interferentes têm sido responsabilizadas pela falta de identificação dos efeitos benéficos.

Conclusão: diante das evidências científicas pautadas em grande parte dos estudos, acredita-se que a ausência da amamentação seja um possível fator de risco modificável para diabetes tipo 1 e tipo 2. Estratégias que visem à promoção e ao suporte ao aleitamento materno devem ser adotadas por profissionais de saúde devidamente treinados como forma de prevenir a manifestação da doença.

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Introduction

Diabetes mellitus (DM) is among the leading causes of morbidity and mortality, and its worldwide prevalence has increased rapidly, especially in developing countries.¹ For Brazil, in 2010 the overall estimated prevalence, including type 1 DM (T1DM) and type 2 DM (T2DM) in adults, was 6.4% (approximately 12 million). It should be noted, however, that the increasing prevalence of the disease is found worldwide. There were 371 million diabetics worldwide in 2012. It is estimated that in 2030, approximately 552 million individuals will have diabetes. This is equivalent to one diabetic patient for every ten adults; for that number to be reached, three new cases will be identified every 10 seconds.²

Although T1DM is less common than T2DM, it has been increasing every year, both in developed and in developing countries. The worldwide prevalence of T1DM is 0.1% to 0.3%, with 78,000 new cases every year, especially among young individuals (< 5 years).² T2DM affects approximately 7% of the general population.²

Diabetics are at increased risk of developing cardiovascular disease, neuropathies, and nephropathies, with decreased quality of life and survival.³ According to the International Diabetes Federation, diabetes caused 4.8 million deaths in 2012.² Due to the magnitude of the disease and its impact on public health, identifying measures to prevent its occurrence is of great interest. It is believed that breast milk is able to have a positive impact on health by preventing the manifestation of diseases such as DM.⁴

In T1DM, the autoimmune destruction of pancreatic β cells is genetically transmitted. However, it appears that not all individuals that have the gene develop the disease. This fact suggests the existence of environmental factors that can control its manifestation. It is believed that the early use of cow's milk, a highly allergenic food,⁵ and the absence of breastfeeding are responsible for triggering the abovementioned autoimmune process.⁶ The destruction of

β cells occurs on average for ten years, coinciding with the peak incidence of the disease, which occurs between the ages of 10-14 years.⁷

The association between breastfeeding and T1DM has been demonstrated in a case-control study involving 1,390 preschoolers. That study demonstrated that receiving breast milk for five months or longer acted as a protective factor against diabetes (OR: 0.71, 95%CI: 0.54-0.93).⁸ Thus, a considerable proportion of diabetes risk was explained by modifiable exposure, and is potentially preventable. The protective effect of human milk has been linked to its anti-infective properties and because its use prevents early exposure to other infectious agents present in other types of milk.⁹⁻¹¹ However, some researchers have contested this association.^{12,13}

Individuals that were breastfed have lower rates of obesity and T2DM than those fed infant formula.^{14,15} The investigated benefits were proportional to the duration of breastfeeding.^{16,17} Such effects have been attributed to appetite regulation and reduced weight gain in breastfed children and/or effects of nutrients or bioactive constituents present in human milk.¹⁸ Breastfeeding as protective practice against T2DM has also been demonstrated in several other studies,¹⁹⁻²¹ but not in all.^{18,22} The divergence in the results of these studies may reflect the existence of biases and confounding factors.

Therefore, a critical review of studies published on the subject was conducted in order to clarify the influence of breastfeeding on the risk of T1DM and T2DM development. This analysis also aimed to identify possible dietary strategies that can be implemented to prevent disease onset.

Methods

A literature review was performed after research in the following electronic databases: Scientific Electronic Library Online (SciELO), Latin American and Caribbean Health

Sciences (LILACS), Medical Literature Analysis and Retrieval System Online (MEDLINE), SciVerse Scopus (Scopus), and the Virtual Health Library (VHL). The search prioritized studies published in the last ten years on the subject. However, studies considered important and used as reference in the most recent articles were searched for additional review material.

The following key words and their corresponding Portuguese words were used in the search: breastfeeding (aleitamento materno), breast milk (leite do peito), lactating (lactação); early infant feeding (alimentação na infância); complementary feeding (alimentação complementar), diabetes mellitus (diabetes mellitus), type 1 diabetes (diabetes tipo 1), and type 2 diabetes (diabetes tipo 2). Using the term "breast-feeding", 29,069 published studies were identified. However, by including the terms "diabetes", a total of 52 articles were retrieved. Of these, 21 were analyzed (nine for T1DM and 12 for T2DM). The remaining articles were discarded, as they did not specifically address the issue.

Breastfeeding and the manifestation of T1DM

Borch-Johnsen et al., in 1984, were the first to observe that breastfeeding appeared to have a protective effect against T1DM, preventing or delaying the onset of this disease. It is proposed that the presence of antimicrobials and anti-inflammatory agents, as well as substances that promote the maturation of the immune system in human milk exert a protective effect against T1DM.²³

In animals prone to diabetes, offering prolonged and exclusive breastfeeding protected them against autoimmune diabetes, whereas intake of solid foods completely abolished this protective effect. It was found that breastfeeding is correlated with high levels of T-cells and low levels of inflammatory cytokines such as interferon- γ , interleukin-4, and interleukin-10.²⁴ Epidemiological studies in humans also indicate the existence of a similar association.²⁵⁻²⁸ The results of these studies suggest that proper nutrition during the first months of life prevents the manifestation of the disease. However, these positive effects were not identified by some authors.^{13,29}

It appears that early exposure to cow's milk increases the chance of acquiring T1DM when compared to exclusive breastfeeding up to at least four months after birth.³⁰

A meta-analysis (17 case-control studies) evaluated the association between diet in childhood and the risk of developing T1DM. A weak effect was observed between never having been breastfed (OR: 1.13, 95% CI: 1.04 to 1.23), and a moderate effect for infant formulas (OR: 1.38, 95% CI: 1.18 to 1.61) and use of cow's milk before 3 months of age (OR: 1.61, 95% CI: 1.31 to 1.98) and the risk of disease manifestation. It was also found that the effect for populations with low prevalence of breastfeeding was similar to those that had never been breastfed. It is noteworthy that these effects were not observed in populations with high rates of breastfeeding, as well as the lack of association between having been breastfed and never having received breast milk with T1DM in populations in which the prevalence of breastfeeding is low. Thus, in case-control studies, differences in

the prevalence of diabetes and breastfeeding need to be assessed and considered in the design of each study.³¹

In a recent meta-analysis comprising 43 studies (two cohort and 41 case-control studies) and a total sample of 9,874 patients with T1DM, it was observed that exclusive breastfeeding for more than two weeks reduced by 15% the risk of disease and a small reduction was identified in response to breastfeeding (exclusive or non-exclusive) for more than 3 months. It is possible that this difference may have occurred because of the accuracy of the information provided by the mothers and obtained by recall, from early lactation compared to later stages. The difficulties recalling feeding practices in early life is considered an important bias factor that can affect study results.³²

Current evidence of another meta-analysis (27 case-control studies and one cohort) showed seven studies that indicated that breastfeeding for a short period of time or its absence can be a major risk factor for T1DM. The results of five other studies also indicated that, compared with healthy children, the diabetics either had not been breastfed or had been for a short period of time. Additionally, five studies showed an increase in the risk for T1DM associated with early introduction of cow's milk and other human milk substitutes. However, in five other studies, there was a weak association or no association between the disease and the short period of breastfeeding or early introduction of cow's milk. One study showed an inverse association between breastfeeding and the risk of T1DM.³³

It is noteworthy that in all mentioned meta-analyses, the authors state that the weak association sometimes found between breastfeeding and T1DM may reflect the presence of methodological problems related to the reliability of the data analyzed in the studies. The lack of information or details on breastfeeding duration, whether exclusive or not, use of infant formulas and cow's milk, as well as the age of introduction of complementary foods, are some of these previously reported problems.

In a study conducted in Campina Grande, Brazil, with 128 children and adolescents, it was observed that 84.4% of diabetic children had been exposed to cow's milk before four months of age, whereas in the control group, this percentage was 64.1%. In the multivariate analysis, a significant association was found between early exposure to cow's milk and diabetes (OR: 4.09, 95% CI: 1.19 to 14.04).³⁰

Another study, involving 200 T1DM children (2-6 years) in Saudi Arabia, showed an association between T1DM and prolonged consumption of cow's milk (OR = 4.3), short duration of breastfeeding (OR = 3.5), and excessive consumption of cow's milk (OR = 2.4).³⁴

It is believed that bovine serum albumin is one of the possible factors responsible for triggering the autoimmune process involved in the manifestation of T1DM. Antibodies to this protein were found in patients newly diagnosed with the disease. Important epidemiological evidence also indicates the existence of a strong correlation between the consumption of cow's milk and T1DM incidence in several countries.³⁵ Thus, there is little doubt that the consumption of cow's milk is a trigger for the manifestation of diabetes.

Table 1 shows the summaries of studies that investigated the association between T1DM and duration of breastfeeding.

Table 1 Studies that investigated the association between type 1 diabetes mellitus and breastfeeding.

Study	Design	Sample	Age at assessment	Type and duration of breastfeeding	Data collection method	Adjustment for confounding factors	Results
Collado-Mesa & Díaz-Díaz ¹²	Descriptive, retrospective	Cuba N = 263	?	Not assessed, one to two months and three to 44 months (does not inform whether it was exclusive)	Cases registered in national database	-	No association
Macedo et al. ¹⁰	Case-control, retrospective	Brazil N = 124 (47 diabetics and 77 without the disease)	?	The duration of breastfeeding was analyzed before introduction of cow's milk	Patients with previous diagnosis followed at outpatient clinic	-	Inverse association verified for females. Mean time of exclusive breastfeeding in the study group = 2.1 months vs. control = 3.7 months, p = 0.0449.
Rosenbauer et al. ²⁸	Case-control, retrospective	Germany n = 760 cases/1,871 controls	11-14 years	Breast milk: \geq five months versus < two weeks	Cases registered in national database	Additional consumption of cow's milk, family history of T1DM, socioeconomic status, maternal age, birth weight, parity	Breastfeeding \geq 5 weeks was a protective factor against T1DM (OR: 0.71 (CI: 0.54-0.93))
Viner et al. ¹³	Longitudinal, self-report	England, Scotland, Wales and Northern Ireland n = 11,261	5, 10, and 30 years	Was not breastfed; \geq three months, and < three months	Self-report of participants at 30 years of age	-	No association
Leal et al. ¹¹	Descriptive study mother's report	Brazil n = 33 T1DM	?	Was not breastfed, was breastfed < 1 month, or up to one, two, three, four, five, or six months.	Patients with a previous diagnosis followed as outpatients	-	Association verified for early weaning (breastfeeding < six months) and presence of diabetes (30.6% of the sample were breastfed for less than one month and only 12.1% reached six months)

CI, confidence interval; OR, odds ratio; T1DM, type 1 diabetes mellitus.

After analyzing the results of these studies, it appears that there is a controversy on the role of human milk in the development of T1DM.

Although the findings of the study by Leal et al.¹¹ indicated the existence of a positive association between breastfeeding and T1DM, the study lacked a control group. Controls are essential to mitigate the possible effects exerted by confounding variables.

Another difficulty to consider breastfeeding causative of T1DM is associated with the date of onset of pancreatic β -cell destruction, which starts at an early age in children with a genetic predisposition to the disease.³⁶ Thus, this destruction can start many years before the disease diagnosis, and the associations observed in the studies may reflect the effects of other precipitating factors of disease, not necessarily of promoters of the autoimmune process.³⁷

There is reason to believe that the development of chronic diseases of infectious or immunological etiology may be influenced by the type of feeding in the first year of life. Despite the controversies in the study results, the promotion of breastfeeding rather than the use of cow's milk should be encouraged in the first year of life.

Maternal breastfeeding and T2DM manifestation

The reported evidence on the effects of breastfeeding by the Agency for Healthcare Research and Quality highlights, among other benefits associated with breast milk, the protection against T1DM and T2DM,³⁸ which has been reinforced by other authors.³⁹

Children who receive breast milk have a lower risk of being overweight during childhood, adolescence,⁴⁰ and adulthood.⁴¹ The World Health Organization conducted a meta-analysis that included 39 studies published in the past 40 years. The results of this study indicated that breastfed children were less likely to become obese (OR: 0.78, 95% CI: 0.72 to 0.84), even after adjusting for parental nutritional status, socioeconomic status, and birth weight.¹⁵ Recently, the breastfeeding protection against overweight was also confirmed by other authors.⁴²

Moreover, this practice was associated with a 10% to 20% decrease in the risk of cardiovascular events (coronary heart disease and stroke) in women participating in the Nurses' Health Study.⁴³ Conversely, a study involving men showed no association between breastfeeding and risk factors or cardiovascular mortality.⁴⁴ In this study, the authors once again attributed the lack of evidence to the mothers' memory biases, as the evaluation of breastfeeding was performed decades after birth.

In one study, a prevalence of 1.2% of T2DM was found in breastfed individuals, when compared to 3% in those who had not been breastfed, with no significant difference.⁴⁵ According to the authors, this result was possibly due to the low prevalence of diabetes in the studied population.

In one cohort (n=405) there was a decrease of 0.12% in glycated hemoglobin levels in non-diabetic adults that had been breastfed when compared to those that had been formula-fed. Although this reduction was small, the authors emphasized its importance in terms of public health. It was also observed that breastfeeding was inversely associated with the development of atherosclerosis.⁴⁶

Breast milk results in greater satiety than infant formulas, preventing excessive weight gain during childhood. Therefore, this type of milk protects against the development of obesity and consequently, of T2DM.¹⁴ The protective effect of breastfeeding was also observed by other authors.^{13,20}

However, this association has not been observed in some other studies.^{18,22} Nevertheless, according to Davis et al.,²² this fact might be due to the use of the retrospective method to investigate the history of breastfeeding.

Another limitation of that study was the small sample size, as the subjects were divided into breastfeeding duration categories, and there were only eight subjects in the six to 12 months range. These facts may have masked the association between breastfeeding and T2DM.

In the study by Fall et al.,¹⁸ the absence of evidence on the effect of breastfeeding duration on the manifestation of T2DM or adiposity was attributed to the lack of a single definition for exclusive breastfeeding among studies. It is also believed that the association between breastfeeding and T2DM may be affected by the "dose response" effect, that is, the more breast milk the child receives, the lower the risk of developing the disease. However, obtaining reliable information on the amount of breast milk intake and the intake of complementary foods may not occur, thus compromising the reliability of study results. It is important to know the genetic predisposition of the parents, to help separate genetic effects from those resulting from inadequate food supply to the child.⁴⁵

Table 2 shows the summaries of studies that investigated the association between T2DM and duration of breastfeeding.

It is believed that the protection of breastfeeding against overweight and T2DM is associated with its biochemical constituents and their differentiated nutritional composition. Some bioactive substances can promote energy balance by reducing fat deposition and favoring desirable metabolic responses. Human milk contains docosahexaenoic acid (DHA). Further, breast milk contains adequate amounts of polyunsaturated fatty acids (PUFAs) to ensure an adequate number of insulin receptors in the child's brain, necessary to maintain normal glycemic metabolism.⁴⁷

It can be observed that the phospholipid membranes of breastfed children have significantly higher amounts of DHA and other PUFAs than those not breastfed. It is believed that low concentrations of DHA and PUFAs can result in insulin resistance.¹⁴

High levels of basal and post-prandial insulin and neotensin (which inhibits insulin secretion and stimulates glucagon secretion) have been reported in formula-fed infants compared with breastfed infants.⁴⁸ Such differences may lead to the development of insulin resistance and T2DM.

It is noteworthy that most of the authors of the studies analyzed in this review did not report the duration of breastfeeding or provide information on complementary feeding (Table 2). Most of these studies were performed in developed countries, where mothers who follow the nutritional guidelines tend to have high levels of education and income. Analyses of data from countries of low- and middle-income can help identify the effects of confounding factors, since the association between infant feeding practices and socioeconomic class differs among them.¹⁸

Table 2 Studies that investigated the association between type 2 diabetes mellitus and breastfeeding.

Study	Design	Sample	Age at assessment	Type and time of breastfeeding	Data collection method	Adjustment for confounding factors	Results
Young et al. ¹⁶	Case-control	Canada n = 46 (cases) n = 92 (two controls for each case)	< 18 years	Did not receive breast milk, < six months, ≥ six months	Retrospective report by mother	Gestational diabetes, alcohol consumption during pregnancy, smoking during pregnancy, birth weight, maternal nutritional status	Children breastfed for ≥ six months were less likely to develop T2DM compared with those who received breast milk < six months (OR: 0.36, 95% CI: 0.13 to 0.99)
Owen et al. ¹⁴	Systematic review	Seven studies (maternal breastfeeding, formula, and diabetes) n = 76,744 (Australia, Finland, Sweden)	1-71 years	The classifications of exclusive breastfeeding varied between studies and were kept in the analyses as previously classified	The studies defined T2DM in different ways: oral glucose tolerance test - 75g, fasting glucose, post-load or fasting glucose, data collection from questionnaires	Three studies had information about relevant confounding factors (birth weight, family history of diabetes, socioeconomic status, individual and maternal nutritional status)	Individuals who were breastfed were less likely to have T2DM (OR: 0.61, CI: 0.44-0.85). ORs were similar before and after adjustment
Davis et al. ²²	Retrospective for breastfeeding and cohort for nutritional status	Latin Americans n = 240	8-13 years	Did not receive breast milk, < six months, ≥ six months and < 12 months, ≥ 12 months	The study evaluated the risk of T2DM by intravenous glucose tolerance test	Gestational diabetes mellitus, age, gender, and body composition	There was no significant effect of breastfeeding on the risk factors for T2DM
Mayer-Davis et al. ¹⁹	Case-control retrospective	USA n = 80 with T2DM n = 167 (control)		Did not receive breast milk, ≥ six months, and < six months	Retrospective mother's report	Age, gender, current BMI, ethnicity, birth weight, maternal diabetes, family history of diabetes, maternal age, pre-gestational BMI, maternal schooling, smoking during pregnancy, consumption of alcohol during pregnancy	Individuals who were breastfed were less likely to have T2DM compared to those who were never breastfed (OR: 0.26, 95% CI: 0.15 -0.46). Associations remained after adjustment (OR: 0.4, 0.19 to 0.99); however, when BMI was added to the model the association was attenuated (OR: 0.82, CI: 0.30-2.30), suggesting possible mediation through the current weight of the child. * The analyses that incorporated the duration of breastfeeding, even after adjustment, showed a dose response effect (test of trend: p < 0.0001). The results were similar among races/ethnicities (Hispanic, non-Hispanic white, non-Hispanic black).

Table 2 (Continued)

Study	Design	Sample	Age at assessment	Type and time of breastfeeding	Data collection method	Adjustment for confounding factors	Results
Madsen et al. ²⁰	Cross-sectional with analysis of data from a cohort	Denmark n = 265	9 months	Did not receive breast milk, \leq two times/day, or \geq three times/day Breastfeeding up to 9 months of age (yes or no)	The study evaluated the risk of T2DM through the glycemia and insulin levels	Gender, breastfeeding up to 9 months, duration of fasting and energy contained in the meal before fasting for the test, diet, skin folds, body weight, height, and BMI at 9 months	Insulin levels were lower in the group breastfed until 9 months compared to non-breastfed (23.7 pmol/L versus 37.0 pmol/L, $p < 0.042$), with considerable low concentrations when breastfed more times per day. Glucose levels did not differ
Fall et al. ¹⁸	Analysis of data of five prospective cohorts	Brazil, Guatemala India, Philippines, and South Africa n = 10,912	15-41 years	Only one study had information on exclusive breastfeeding	Data collection on breastfeeding was retrospective in all studies	Analyses were adjusted for socioeconomic status, schooling, age, smoking, ethnicity, housing in urban or rural area, and birth weight	There was no association.
Veena et al. ²¹	Cohort	India n = 518	5 and 9.5 years	< three months, three to five months, six to eight months, nine to 11 months, 12 to 17 months, \geq 18 months	Mother's report	The analyzes were adjusted for gender, age, current BMI, income, parental level of schooling, urban or rural residence, birth weight, and gestational diabetes	Prolonged breastfeeding was associated with low levels of insulin and HOMA-IR at 5 years, but not at 9.5 years. The associations were independent from potential confounding factors.

BMI, body mass index; CI, confidence interval; DMT2, type 2 diabetes mellitus; HOMA-IR, homeostatic model assessment of insulin resistance.

It is worth mentioning that, for ethical reasons, the vast majority of available studies involving human subjects on the benefits of alternative forms of feeding are observational, which does not prove the existence of a cause-and-effect association. In these studies, the small number of exclusively breastfed children assessed can also be an important limiting factor to obtain the statistical power necessary to detect beneficial effects.⁴⁵

In low and middle-income countries, even though breastfeeding tends to be a common practice, many mothers introduce complementary foods and terminate breastfeeding early.⁴⁹ Obesity, diabetes, and cardiovascular disease are increasing fast in these countries.⁵⁰ Therefore, the promotion of healthy eating habits in childhood with exclusive breastfeeding maintained up to 6 months and as a complement until at least the age of 2 years is a low-cost strategy that can positively affect the child's health throughout life.

Final considerations

Although there is still no consensus in the scientific community, evidence available to date shows that lack of breastfeeding is a possible modifiable risk factor for the manifestation of both T1DM and T2DM. The benefits of breastfeeding have been attributed to bioactive substances, which promote the maturation of the immune system, reduce insulin resistance, and prevent excessive weight gain during childhood.

In order to answer existing questions on the actual effects of inappropriate feeding practices, well-designed longitudinal studies are needed, with clearer criteria for the selection of participants in these studies and adjustment for potential confounding factors, aiming to elucidate the possible mechanisms responsible for the protective impact of breastfeeding on DM manifestation. It is important that future studies identify the duration and exclusivity of breastfeeding in order to prevent such manifestation in individuals genetically predisposed to the disease.

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Conflicts of interest

The authors declare no conflicts of interest.

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