Published in final edited form as:
*Curr Nutr Rep*. 2014 December 1; 3(4): 345–354. doi:10.1007/s13668-014-0103-5.

# Diet, lifestyle, and genetic risk factors for type 2 diabetes: a review from the Nurses' Health Study, Nurses' Health Study 2, and Health Professionals' Follow-up Study

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## Abstract

The epidemiological evidence collected from three large US cohorts (Nurses' Health Study, Nurses' Health Study 2, and Health Professionals' Follow-up Study) has yielded important information regarding the roles of overall diet, individual foods and nutrients, physical activity and other lifestyle factors in the development of type 2 diabetes. Excess adiposity is a major risk factor for diabetes, and thus, maintaining a healthy body weight and avoidance of weight gain during adulthood is the cornerstone of diabetes prevention. Independent of body weight, the quality or type of dietary fat and carbohydrate is more crucial than the quantity in determining diabetes risk. Higher consumption of coffee, whole grains, fruits, and nuts is associated with lower risk of diabetes, whereas regular consumption of refined grains, red and processed meats, and sugar-sweetened beverages including fruits juices is associated with increased risk. Dietary patterns rich in fruits and vegetables, whole grains, and nuts and legumes but lower in red and processed meats, refined grains, and sugar-sweetened beverages are consistently associated with diabetes risk, even after adjustment for body mass index. The genome-wide association studies conducted in these cohorts have contributed substantially to the discoveries of novel genetic loci for type 2 diabetes and other metabolic traits, although the identified common variants explain only a small proportion of overall diabetes predisposition. Taken together, these ongoing large cohort studies have provided convincing epidemiologic evidence that a healthy diet, together with regular

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**Compliance with Ethics Guidelines**

**Human and Animal Rights and Informed Consent**

This article does not contain any studies with human or animal subjects performed by any of the authors.

**Conflict of Interest**

Andres V. Ardisson Korat, Walter C. Willett, and Frank B. Hu declare that they have no conflict of interest.

physical activity, maintenance of a healthy weight, moderate alcohol consumption, and avoidance of sedentary behaviors and smoking would prevent the majority of type 2 diabetes cases.

**Keywords**

Diet; Dietary Patterns; Western diet; Prudent diet; Physical Activity; Type 2 Diabetes mellitus; Body Mass Index; Nurses Health Study; Health Professionals Follow-up Study

## Introduction

The most recent estimates by the International Diabetes Federation indicate that in 2013 382 million adults aged 20 – 70 worldwide had Type 2 diabetes Mellitus (T2DM) with 80% of the affected living in low and middle-income countries.[1] This number is expected to rise to 592 million by 2035 (a 55% increase) with projected increases in every region of the world.[1] Areas particularly affected by this disease are China and India, where the prevalence of T2DM has increased even though body mass index (BMI) has not increased to the same extent.[2] It is estimated that in 2013 diabetes caused 5.1 million deaths alone and that half of those came from people under 60.[1]

T2DM is caused by both environmental and genetic factors as well as gene-environment interactions. Prospective cohort studies have contributed substantially to our understanding of the role of these factors in the development of T2DM. In this paper, we briefly summarized the role of a multitude of factors in the development of T2DM including diet, lifestyle, and genetics from the information collected from nearly 100 prospective cohort analyses or nested case-control studies from these three large cohorts conducted at Harvard School of Public Health and Brigham and Women's Hospital.

## Description of the Cohorts Studies

The Nurses' Health Study (NHS) was established in 1976 by recruiting 121,700 female nurses aged 30 to 55 who responded to a questionnaire with information related to their health, lifestyle practices and occurrence of chronic diseases. The Nurses' Health Study 2 was established in 1989 by recruiting 116,671 participants who were 24 to 44 years of age.[3] The Health Professionals' Follow-up Study (HPFS) started in 1986, when 51,529 male health professionals, who were 40 – 75 years of age at recruitment in 1986.[4] For these three cohorts, information is updated biennially with mailed questionnaires that include food frequency information (FFQ).[5,6] Incident cases of T2DM are ascertained by self-reports on these questionnaires and confirmed by supplementary information collect about the diagnosis, using the following criteria: (1) manifestation of classic symptoms such as excessive thirst, polyuria, weight loss and hunger, in conjunction with elevated fasting or non-fasting glucose levels (2) asymptomatic but elevated plasma glucose in two separate occasions or abnormal glucose tolerance test results and (3) receiving any hypoglycemic treatment for diabetes. Medical records were obtained for a subset of the subjects reporting a diabetes diagnosis to validate the information obtained by the supplemental questionnaire.[5]

## Anthropometric Factors

Excess adiposity (usually reported as BMI or waist circumference) remains as one of the strongest risk factors for T2DM in cohorts of both men and women. The risk of T2DM increases as BMI or waist circumference increases.[7–9] Furthermore, the risk is highly sensitive to steady weight changes during adulthood, including a large reduction in risk with weight loss.[10–12] Cyclical weight changes are also associated with increased risk.[13]

## Dietary Factors

### Individual Nutrients

**Carbohydrates:** In our cohorts, we have consistently shown an association between carbohydrate quality, typically measured as Glycemic Index (GI) or Glycemic Load (LD), and risk of T2DM. While the mechanism has not been elucidated, it is likely due to excessive secretion of insulin or toxicity of β-cells due to hyperglycemia.[14–17] The most comprehensive study to date from the three cohorts showed that participants in the highest quintiles of GI and GL (adjusted for total energy) had a significantly higher risk of T2DM than those in the lowest quintile.[18] This conclusion was supported by a meta-analysis published with the study which included cohorts from the US, Australia, and Europe.[18]

**Fat:** Total dietary fat intake was not associated with risk of T2DM in the NHS and HPFS when comparing to equivalent energy substitutions from carbohydrate.[4,19] However, the type of fat seems to have an important effect: whereas energy intake from total fat, saturated fat or monounsaturated fat was not associated with risk of T2DM, an increase in energy intake from polyunsaturated fat was inversely associated with risk of T2DM and higher levels of *trans* fatty acids was associate with higher diabetes risk.[19] A study from the NHS found no association for total fat intake but an inverse relationship between vegetable fat intake and risk of T2DM, especially linolenic acid and total polyunsaturated fat intake.[20] These findings are consistent with the results from the Women's Health Initiative randomized trial, which also found no significant effects of total fat intake (low-fat diet vs. control) on the incidence of T2DM[21]. For men (HPFS), there were no significant associations between total fat or type of fat when comparing extreme quintiles of intake, but linoleic acid was inversely associated with risk of T2DM among younger men.[4] A review of epidemiological studies and controlled dietary interventions arrived at the same conclusion: the replacement of saturated and *trans* fatty acids with unsaturated fat seems to help prevent T2DM.[22]

### Micronutrients

**Vitamin D and Calcium:** In a nested case-control study from NHS, women in the top quartile of plasma 25-hydroxyvitamin D (25-OHD) had significantly lower odds of developing T2DM than women in the bottom quartile of OHD.[23] However, a prospective study from the same cohort found little association between total vitamin D intake and risk of T2DM, although vitamin D intake from supplements appeared to be inversely associated with risk of T2DM.[24] Furthermore, the combined intake of calcium and vitamin D (highest quintiles for both nutrients) was associated with a 33% reduction in risk of T2DM.[24]

**Magnesium:** Magnesium intake was associated with lower risk of T2DM in both men and women (from HPFS and NHS)[20,25]. Good sources of magnesium include whole grains, nuts, and green leafy vegetables which are foods associated with reduced risk of T2DM.[25] These associations are consistent with the results of a meta-analysis of prospective cohort studies including populations from the US (NHS and HPFS included), Finland, and Australia in which greater magnesium intake was associated with lower risk of T2DM.[26]

**Zinc:** One prospective cohort analysis from NHS found a modest inverse association between total zinc intake and zinc from food intake and risk of T2DM after comparing extreme quintiles and also a significant negative association with the ratio of dietary zinc to iron.[27] Although the mechanism of this association is yet to be explained, zinc is part of the structure of insulin and it has been linked to its biosynthesis and storage. Zinc may also play a role in protecting β cells from oxidation.[27]

**Selenium:** Selenium concentration in toenails (a biomarker of long-term selenium intake) in a subset of the NHS and HPFS cohort was inversely associated with risk of T2DM.[28]

**Flavonoids:** In a prospective analysis from the three cohorts, an inverse association was seen between anthocyanin intake and incidence of T2DM.[29] Anthocyanins are found in blueberries and apples and pears, and comparison of extreme intake categories of these fruits yielded inverse associations consistent with the flavonoid analysis. Total flavonoid intake and other flavonoid subclasses were not associated with T2DM.[29]

## Foods and Food Groups

**Fruits and Vegetables:** Multiple analyses from the three cohorts have found that habitual intake of individual foods as well as aggregate dietary patterns are associated with the risk of T2DM independent of adiposity and weight change. An analysis from NHS 2 found that increasing whole fruit intake of ≥3 servings/day was associated with a lower risk of T2DM, whereas the same increase in fruit juice consumption was linked to an increased risk.[30] Total fruit and vegetable intake was not associated with T2DM although an increase of 1 serving per day of green leafy vegetables was associated with a modest risk reduction.[30] The protective effect of green leafy vegetables was also reported in a meta-analysis of cohorts in the US, Finland, and China.[31]. A study that pooled the data from the three cohorts found a significant inverse association between total fruit consumption and lower risk of T2D.[32] Additionally, the study examined individual fruits and found apparent protective effects of blueberries, grapes and raisins, bananas, apples and pears and null associations for prunes, peaches plums and apricots, oranges and strawberries. Consistent with the other analyses, there was a positive association between the fruit juice consumption and risk of T2DM.[32] A recent meta-analysis that included cohorts from the US, Europe, and China found an inverse association between fruit and vegetable consumption and risk of T2DM, but no associations with only fruits or vegetables. Only green leafy vegetables as a subgroup had a significant inverse association.[33]

**Dairy Products:** In NHS 2, dairy product consumption during adolescence was associated with a significantly lower risk of T2DM in adulthood when comparing extreme intake

quintiles.[34] A significant inverse association between dairy consumption and risk of T2DM in the HPFS.[35] When classifying by fat content, the apparent protective effect was present for low-fat dairy products but no association was found for high fat dairy.[35]

**Red and Processed Meats:** Strong evidence from the three target cohorts has shown a positive association between red meat consumption and risk of T2DM. In the NHS2 red meat, total processed red meats and individual products (bacon, hot dogs) were strongly associated with increased risk of T2DM.[5] For men and women studied separately, the group consuming ≥5 servings of processed red meat per week (compared to the lowest group) had markedly higher risk of T2DM.[3,4] Pooled data from the three cohorts showed that the risk increased significantly for every serving (50 g) of both unprocessed red meat and processed red meat[36]. Also, increases of ≥0.5 serving per day in overall red meat intake over a 4-year period were associated with elevated risk of T2DM by 30% after adjusting for BMI and weight changes and reducing red meat intake in the same proportion was associated with lower risk.[37] While total iron intake was not associated with risk of T2DM, heme iron from red meat was associated with higher risk of T2DM when comparing extreme quintiles of intake for both men and women.[38,39] These results are consistent with the conclusion of a meta-analysis of prospective cohort studies in the US, Europe, and Japan that intake of red meat and processed red meat, but not total meat intake (poultry and fish were included), was associated with increased risk of T2DM.[40] It has been hypothesized that elevated heme iron intake may interfere with glucose metabolism or promote oxidative stress, which may affect β-cells in the pancreas.[40]

**Whole Grains:** Whole grain (WG) consumption has been documented to have a strong inverse association with risk of T2DM,[41,42] although the effect of refined grain consumption on risk of T2DM from these analyses is less conclusive. The apparent protective effect of WG consumption was observed in both NHS and NHS2 and after pooling the results from 6 cohort studies; it was estimated that for every two-serving per-day increment in WG consumption, the risk of T2DM decreased by 21%.[43]

**Rice:** Consumption of brown and white rice and its relationship with T2DM has been examined in a pooled analysis of our three cohorts.[44] Comparing extreme quintiles, white rice was positively associated with an 17% increased risk of T2DM whereas brown rice was associated with an 11% risk reduction. Also, substituting 50 g per day of uncooked white rice with brown rice was associated with a 16% diabetes risk reduction. Substituting the same amount of white rice with other whole grains also had an apparent protective effect.[44] A meta-analysis showed a stronger positive association between white rice and T2DM in Asian populations, in which white rice is a staple food, than Western populations.[45]

**Potato and french fries:** Consumption of potatoes and fries was positively associated with risk of T2DM in the NHS after adjusting for BMI and other covariates.[46] Moreover, the analysis predicted a 30% lower risk of T2DM for the substitution of 1 serving a day of whole grains for 1 serving a day of potatoes.

**Nuts:** Frequent consumption of nuts and peanut butter was inversely associated with T2DM in women from NHS.[47] A more recent analysis from NHS and NHS2 also found an inverse

association between consumption of walnuts at least twice a week versus never/rare consumption and lower T2DM, even after adjustment for BMI.[48]

**Sugar-Sweetened Beverages:** The association between sugar sweetened beverages (SSB) consumption and risk of T2DM has been examined in the three cohorts. A analysis from HPFS found that SSB intake was significantly associated with risk of T2DM,[49] but no significant association between artificially sweetened beverages (ASB) and risk of T2DM was seen in the multivariate-adjusted model. An analysis from NHS2 found that consumption of 1 or more SSB per day significantly increased the risk of T2DM by 83% compared with those who consumed <1 of SSB per month, and excess body weight explained half of the asociation.[50] Another analysis from NHS2 found that, while water consumption was not associated with risk of T2DM, replacement of one serving of SSB with water was significantly associated with lower risk of T2DM.[51] Substituting coffee or milk for SSB also reduced T2DM risk.[51] In the NHS and HPFS both caffeinated and caffeine-free SSB appeared to increase the risk of T2DM.[52] A positive association was observed in a meta-analysis including cohorts from the US, Finland, and China and Singapore, which found that those in the highest quintile of SSB consumption (1–2 serving per day) had a 26% increased risk of T2DM compared with those in the lowest quintile (<1 serving per month).[53]

**Coffee, Tea, and Caffeinated Beverages:** Multiple epidemiological analyses have linked the consumption of coffee with a lower risk of T2DM and this association seems to be independent of the caffeine content. In the NHS2, a significant inverse association was seen between coffee intake and risk of T2DM. This association was also significant for decaffeinated, and instant coffee consumption but not for tea (≥4 cups per day).[54] Similar associations were observed in NHS and HPFS where high intake of both regular and decaffeinated coffee, but not tea, was associated with a lower risk of T2DM.[55] An analysis examining changes in coffee intake over a 4-year period in the three cohorts found that a > 1 cup per day increase in coffee consumption was associated with a 11% lower risk of T2DM and a decrease in ≥2 cups per day was associated with a 17% increase in T2DM risk.[56] These results are consistent with several systematic reviews and meta-analyses that include prospective cohort studies from populations in the US and around the globe.[57–59]

**Alcohol Consumption:** Moderate alcohol consumption (15 – 29g/day) has been associated with lower risk of T2DM in both men and women compared to nondrinkers. In analyses from the NHS and HPFS, the apparent protective effect was not only related to the quantity of alcohol but also the frequency, with a RR reduction of 7% for every day of the week that alcohol was consumed.[60–62] A change in alcohol intake habits of 7.5 g per day over a 4-year period for nondrinkers or light drinkers (≤15 g per day) was associated with a significant decrease in risk of T2DM, although the association was not significant for those already consuming ≥15 g per day.[63] Another analysis from NHS showed that alcohol intake attenuated the positive association between GL and risk of T2DM but it did not modify the association with GI.[64] These results are consistent with a meta-analysis of studies from populations in the US, Europe, Australia, Japan, and Korea where it was shown that alcohol

intake and risk of T2DM share a U-shaped relationship with a nadir of 24 grams per day for women and 22 g per day for men.[65]

**Dietary Patterns—**Dietary quality scores have been developed to characterize overall dietary patterns by intakes of food groups or nutrients. A prospective cohort analysis from HPFS examined the association between four dietary scores and risk of T2DM,[66] including an alternative Healthy Eating Index (aHEI) which assigns points on a 100-point scale to the intake of whole grains, fruits and vegetables as well as lower intakes of saturated fat, red meat, total fat, and cholesterol; the 40-point Dietary Approaches to Stop Hypertension (DASH) score; the 9-point alternative Mediterranean diet (aMED) and the Recommended Food Score (RFS).[66] The analysis found that aHEI, DASH, and aMED scores were significantly associated with a reduced risk of T2DM. There was no association between RFS and T2DM and the DASH score was inversely associated with risk of T2DM independent of other scores when comparing extreme quintiles of diet scores.[66] Other studies from the NHS that derived dietary patterns empirically using principle component analysis found that a Western dietary pattern characterized by a higher intake of red and processed meats, sweets, refined grains, and french fries was associated with a 49% increase in risk of T2DM comparing the highest vs. the lowest quintiles.[5] In a separate analysis of diet and lifestyle risk factors in the development of T2DM from the NHS, women who consumed a diet defined by low GI, low *trans* fats, high cereal fiber and a high ratio of polyunsaturated to saturated fat had a lower risk of T2DM compared to those with a low score for this combination of variables.[67] In men from the HPFS, consumption of a prudent dietary pattern was associated with a modest risk reduction of T2DM and Western diets were positively associated with risk of T2DM.[68] These results are consistent with findings form the Insulin Resistance Atherosclerosis study[69] and the PREDIMED randomized trial where individuals who were at high risk of cardiovascular disease were randomized to either a control group, Mediterranean diet supplemented with extra-virgin olive oil (EVOO) or nuts. Mediterranean diets were effective at reducing the risk of T2DM, especially when supplemented with EVOO.[70,71]

In the NHS 2, women in the highest quintile of a Western dietary pattern during adolescence had a 19% higher risk of developing T2DM than those in the bottom quintile; the prudent dietary pattern during adolescence had no association with diabetes.[72] Western-style diets were associated with biomarkers of inflammation and endothelial dysfunction in a nested case-control in the NHS and NHS2, which in turn have been associated with the development of T2DM.[73,74] With regards to meal frequency, prospective cohort studies from NHS and HPFS found that both men and women who skipped breakfast had a higher risk of T2DM than those who did not skip.[75,76] Furthermore, the association with T2DM was stronger for men who ate irregularly (1–2 meals per day) compared to those who ate three meals per day,[76] whereas the association was not significant for women.[75]

In general, observational evidence from the cohorts of interest and other large epidemiological studies points to diets with higher cereal fiber, polyunsaturated to saturated fat ratio, fruits and vegetables, and coffee and low in glycemic index and load, trans fat, SSBs, and red and processed meats as being protective of T2DM.[77]

## Other Lifestyle Factors

### Physical Activity

Physical activity is one of the most important lifestyle factors in the prevention of T2DM. Prospective analyses from HPFS and both NHS cohorts have shown significant T2DM risk reductions regardless of the type of exercise (weight training or aerobic) and an even stronger protective effect when both were combined.[78,79] Furthermore, the association held considering a wide range of intensity levels of PA, including brisk walking.[80,81] Conversely, sedentary behaviors such as television watching were positively associated with risk of T2DM, where every 2 hour/day increment TV watching and sitting at work were associated with a 14% and a 7% increase in risk of T2DM, respectively.[81]

### Smoking

In our cohorts, exposure to cigarette smoke both passively and actively was associated with increased risk of T2DM when compared to nonsmokers.[62,82,83] The risk of T2DM increased with number of cigarettes consumed per day and the elevated risk persisted in past smokers and decreased with time of quitting.[82] These associations were consistent with findings from the WHI.[84]

### Rotating shift work

In a combined analysis of NHS and NHS2, women who worked extended periods of rotating shift work had a higher risk of T2DM compared to women who did not work shifts, potentially due to glucose deregulation due to disruption of sleep disorders.[85] There was a dose-response relationship between longer duration of shift work and risk of T2DM, and part of the association was mediated through weight gain.[85]

### Snoring and sleep duration

Women in the NHS who snore had a higher risk of T2DM when compared to those who did not snore. It is hypothesized that snoring increases insulin resistance and this is a strong risk factor for T2DM and cardiovascular disease.[86] In the NHS, both long (>=9 hours/day) and short (<=5 hours/day) sleep durations were associated with an increased risk of diabetes incidence.[87] In addition, lower melatonin secretion, an indicator of sleep disruption, was independently associated with a higher risk of developing T2DM.[88]

## Health Related Factors

### Oral Contraceptive Use

In the NHS, current oral contraceptive (OC) use was not associated with risk of T2DM. However, past users had an 11% increased risk of T2DM compared to women who had never used OC. Length of use and time since quitting were not significantly associated with T2DM.[89]

### Hypertensive medications

Thiazide diuretic and β-blocker use was associated with a higher risk of T2DM for both men and women in the three cohorts compared to nonusers; ACE inhibitors and calcium channel blocker use were not associated with T2DM.[90]

### Antidepressant Medications (ADM)

In a prospective analysis from the three target cohorts, ADM use was significantly associated with an increased risk of T2DM in both men and women.[91] Women in NHS who had the highest scores of reported depressive mood had an elevated risk of T2DM compared to women with the lowest scores; the association was bidirectional as women who were diagnosed with T2DM were at higher risk for depression.[92]

### Phobic Anxiety Symptoms (PAS)

The association between PAS and T2DM was examined in a prospective analysis that included the three cohorts. The risk of T2DM increased across categories of PAS measured by Crown-Crisp Index (CCI) after adjusting for depression and major confounding variables.[93]

### Plasma bicarbonate

In a nested case-control study from NHS, women who had plasma bicarbonate above the median level had lower risk of developing T2DM than those below the median. Lower plasma bicarbonate is a biomarker of metabolic acidosis.[94]

### Microbiome metabolites

In a nested case-control study in the NHS and NHS2, urine products related to lignin metabolism (component associated with the consumption of fiber-rich foods), enterodiol and enterolactone, were inversely associated with risk of T2DM.[95]

### Family history, ethnicity, and genetics

Participants of NHS with a family history of diabetes were at significantly higher risk of T2DM than those without a family history of diabetes and were also more likely to have a higher BMI.[96] In terms of ethnicity, the risk of T2DM in women from NHS who identified themselves as Asian, Black, or Hispanic were significantly higher than for those who identified themselves as White.[97] Furthermore, diets high in fiber, polyunsaturated fat and low in *trans* fat and GL were associated with a stronger inverse association for minorities than for whites.[97] The DIAGRAM (Diabetes Genetics Replication And Meta-analysis) Consortium that includes NHS, HPFS, and 40 other international groups have identified more than 50 novel common variants for T2DM.[98] In the NHS and HPFS[99] and meta-analyses of large population-based studies,[100] the cumulative genetic risk score (GRS) calculated by counting the number of diabetes risk alleles did not materially improve the prediction of T2DM beyond traditional risk factors.

Interactions between diet and genetic predisposition to T2DM were observed in the HPFS, where a positive association between the Western dietary and T2DM was much more

pronounced among those with a higher GRS than those with a lower GRS.[101] In addition, carbohydrate quality and quantify significantly modified the association between TCF7L2 variants and risk of T2D in the NHS.[102] In a genome-wide association study from the NHS and the HPFS, genotypes linked to body iron storage were associated with a decreased of T2DM in men but not in women.[103] A nested case-control analysis form the NHS and HPFS found no gene-environment interactions between iron metabolism genotypes and heme iron intake in relation to T2DM.[104]

Genotype scores for dyslipidemia for HDL, but not for LDL were associated with increased risk of T2DM in a nested case-control study from the NHS and the HPFS.[105] Polymorphisms near the Insulin Receptor Substrate 1 (IRS1) gene were associated with risk of T2DM and physical activity appeared to modify this association in women, but not in men.[106] Furthermore, a nested case-control analysis form the NHS showed that women with higher obesity genotype scores had significantly higher risk of T2DM.[107]

## Environmental exposures

Particulate Matter Exposure (PEM): Exposure to PEM was not associated with risk of T2DM in the NHS and HPFS who lived in metropolitan areas. However, living < 50 m from a major road, as a proxy for PEM exposure, was associated with an elevated risk of T2DM compared to those who live > 200 m.[108]

### Bisphenol-A (BPA) and phthalate

In NHS and NHS 2, increased urinary levels of BPA and phthalate metabolites were associated with the risk of T2D among middle-aged, but not older, women.[109]

### Persistent organic pollutants (POPs)

In a meta-analysis of NHS and six other cohort studies, higher urinary levels of total POPs and certain individual POPs were significantly associated with T2DM risk.[110]

### Other factors

Low birth weight in NHS was associated with elevated risk for T2DM compared to the referent group (7.1 to 8.5 lbs.) after adjusting for maternal BMI and history of diabetes.[111] For parous women in NHS2, having a very preterm birth (20 to ≤32 weeks) was associated with an increased T2DM risk when compared to those with regular term pregnancies. Moderate preterm (33 to 37 weeks), term low birth-weight, and macrosomia were not associated with T2DM compared to those with regular term pregnancies.[112] Factors such as age of menarche were explored in an analysis from NHS and NHS2 and found that early menarche (ages ≤ 12) vs. 13 was associated with increased risk of T2DM in adulthood, whereas no association was found for age at menarche ≥ 14.[113] In an analysis combining a prospective examination from NHS and a retrospective design from NHS 2 found that increasing longer duration of lactation was associated with lower risk of T2DM.[114]

## Conclusion

The evidence from the prospective cohort studies included in this review as well as analyses from other cohorts has shown that diet and lifestyle factors play a major role in the development of T2DM. Diets rich in fruits and vegetables, nuts, whole grains, and low in refined grains, red meats, and SSBs have shown a consistent protective association with T2DM. Maintaining a healthy weight, avoiding smoking and engaging in regular physical activity are major lifestyle factors that help prevent T2DM. More than 90% of T2DM cases are potentially preventable by following a healthful diet, having a BMI of ≤25 $m^2$, exercising for at least 30 minutes a day, avoiding smoking, and consuming alcohol in moderation.[67] These data, together with those from randomized controlled trials conducted in high-risk individuals, indicate that diet and lifestyle modification is of paramount importance in preventing T2DM.[115–118] The adoption of a healthy diet and lifestyle, however, requires not only individual behavioral changes, but also changes in the food, built, and social environments.

## Acknowledgement

The diabetes components of the Nurses' Health Study and Health Professionals' Follow-up Study have been mainly supported by NIH grants DK58845, U01HG004399, UM1CA167552, UM1CA176726, and UM1CA186107.

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