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Chapter 1

# The Utility of Vitamins in the Prevention of Type 2 Diabetes Mellitus and Its Complications: A Public Health Perspective

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## 1. Introduction

Type 2 diabetes mellitus (T2DM) is currently considered as a global health problem where about six people die every minute from the disease worldwide. This rate will make T2DM one of the world's most prevalent causes of preventable mortality [1]. T2DM is caused by impaired glucose tolerance (IGT) as a result of insulin resistance and consequential islet β-cell exhaustion, with ensuing insulin deficiency [2]. In individuals with IGT, numerous genetic, host-related, and environmental factors contribute to the progression of insulin resistance to T2DM [3-7]. Obesity, however, is a major cause of insulin resistance [5] and can be complicated by metabolic dysregulation including hypertension and dyslipidemia [known collectively as the metabolic syndrome] which is a precursor of T2DM. The dyslipidemia involves high levels of triacylglycerides and circulating fatty acids originating from the diet or accelerated lipolysis in adipocytes. Direct exposure of muscle cells to these fatty acids impairs insulin-mediated glucose uptake and, therefore, may contribute to insulin resistance [8,9]. Within the last decade, a hypothesis was proposed to explain the pathogenesis of T2DM that connects the disease to a state of subclinical chronic inflammation [10,11]. Inflammation is a short-term adaptive response of the body elicited as a principle component of tissue repair to deal with injuries and microbial infections (e.g., cold, flu, etc.). It can be also elevated in chronic conditions such as peripheral neuropathy, chronic kidney disease and fatty liver. While the influence of fats is well known (see below), current thinking suggests that abnormal levels of chemokines released by the expanding adipose tissue in obesity activate monocytes and increase the secretion of pro-inflammatory adipokines. Such cytokines in turn enhance insulin resistance in adipose and other tissues, thereby increasing the risk for T2DM [12,13]. Together, lipid toxicity and low-grade

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inflammation appear to be major assaults on insulin sensitivity in insulin-responding tissues [9,14,15].

Activation of innate immunity promotes various inflammatory reactions that provide the first line of defense the body invokes against microbial, chemical, and physical injury, leading to repair of damage, isolation of microbial infectious threats and restoration of tissue homeostasis [16,17]. Inherited variations in the degree of innate immune response may determine the lifetime risk of diseases upon exposure to adverse environmental stimuli [18]. Therefore, innate immune responses can be viewed as the outcome of interaction between genetic endowment and the environment [19].

This article was undertaken in an attempt to evaluate the current knowledge linking vitamin intake to attenuating inflammation, and thereby reducing the risk of T2DM and its complications.

## 2. Micronutrients, T2DM and inflammation

Factors that attenuate inflammation could provide an important public health tool to reduce the burden of diseases related to this pathway, such as obesity, T2DM and cardiovascular diseases, in the general population. The feasibility of modulating innate immunity-related inflammation as an approach for the prevention of T2DM is based on reports that evaluated the efficacy of anti-inflammatory pharmaceutical agents on disease manifestation and outcome [12,20].

A therapeutic strategy for T2DM that would act primary on the inflammatory system has been proposed in the form of salicylates, an anti-inflammatory agent long known to have a hypoglycemic effect [21,22]. Nonsteroidal anti-inflammatory drugs (NSAIDs) and cyclooxygenase inhibitors are able to enhance glucose-induced insulin release, improve glucose tolerance, and increase the effect of insulin in patients with T2DM [15,23,24]. In humans, treatment with NSAIDs improved various biochemical indices associated with T2DM [25]. Although these observations support the notion that inflammation plays a pivotal role in T2DM, attenuating inflammation as a strategy for disease prevention in a public health setting will necessitate a substantially different perspective. In this case, a strategy that can be introduced into the general population with the least (if any) side effects and the maximal preventive outcome should be adopted. In this context, a nutritional intervention approach would be a desirable option.

Numerous nutritional factors can modify innate immune-related responses and, subsequently, modify the risk of a range of chronic conditions. With respect to T2DM, the consensus of available information suggests that micronutrient intake modulates the innate immune system [26] and can subsequently influence the predisposition to [and prevention of] disease [26-28]. By virtue of this observation, the hope is that the outcome of nutritional supplementation can be simply monitored via its modifying action on the levels of inflammatory biomarkers. Many micronutrients exhibit well-characterized anti-inflammatory or immunomodulatory functions [25]. Vitamins (e.g., D, E, and C), certain fatty acids (e.g., omega-3 fatty acid) and trace elements (e.g., selenium, zinc, copper and

iron) are known to improve the overall function of the immune system, prevent excessive expression and synthesis of inflammatory cytokines, and increase the 'oxidative burst' potential of macrophages [25]. Vitamin C is the major water-soluble dietary antioxidant anti-inflammatory factor, exerting its actions in the aqueous phase. In contrast, vitamins E and D are lipid-soluble and protect against inflammation in the lipid phase, e.g., adipocytes. Although acting primarily in different phases, these micronutrients can function together by regenerating each other in the reduced form [29]. Indeed, exploring the possibility that supplementation with selected micronutrients can attenuate obesity-related inflammation in order to delay the development of T2DM should be considered alongside existing public health practices to reduce the disease rising rates.

## 3. Vitamin C

Vitamin C (ascorbic acid or ascorbate), an essential nutrient, is a 6-carbon lactone and the primary hydrophilic antioxidant found in human plasma [30]. Circulating concentrations of ascorbate in blood are considered adequate if at least 28 μM, but they are considerably higher in most cells due to active transport. The daily recommended dietary allowance for vitamin C is 75 mg for women and 90 mg for men, with an additional 35 mg for smokers due to the higher metabolic turnover of the vitamin in this group as compared to non-smokers [31]. Ascorbate appears in the urine at intakes of roughly 60 mg/day. However, the results of a depletion/repletion study in healthy young women showed that ascorbate plasma and white blood cell concentrations only saturate at intakes of 200 mg/day or higher [32]. These results suggest that the current dietary recommendations may not provide tissue-saturating ascorbate concentrations [33]. Indeed, epidemiologic findings suggest that serum ascorbic acid deficiency may be relatively common. For example, a recent cross-sectional survey of healthy young adults of the Toronto Nutrigenomics and Health (TNH) Study reported that 1 out 7 individuals is deficient in serum ascorbic acid [34].

Vitamin C has an important role in immune function and various oxidative and inflammatory processes, such as scavenging reactive oxygen species (ROS), preventing the initiation of chain reactions that lead to protein glycation [31;35] and protecting against lipid peroxidation [31, 36]. The oxidized products of vitamin C, ascorbyl radical and dehydroascorbic acid, are easily regenerated to ascorbic acid by glutathione, NADH or NADPH [31]. In addition, ascorbate can recycle vitamin E and glutathione back from their oxidized forms [31, 33]. For this reason, there has been interest in determining whether vitamin C might be used as a therapeutic agent against the oxidative stress and subsequent inflammation associated with T2DM.

A variety of epidemiologic studies have assessed the effect of vitamin C on biomarkers of oxidation, inflammation and/or T2DM risk [30, 37-42]. A large cross-sectional evaluation of healthy elderly men from the British Regional Heart Study reported that plasma vitamin C, dietary vitamin C and fruit intake were inversely correlated with serum CRP and tissue plasminogen activator [tPA], a biomarker of endothelial disfunction [134]. However, only plasma vitamin C was inversely associated with fibrinogen levels [30]. Another cross-sectional study of adolescents aged 13-17 found inverse associations between intakes of

fruit, vegetables, legumes and vitamin C and urinary $F_2$-isoprostane, CRP, and IL-6 [43]. A recent cross-sectional evaluation of healthy young adults from the TNH Study demonstrated that serum ascorbic acid deficiency is associated with elevated CRP and other factors related to the metabolic syndrome such as waist circumference, BMI and high blood pressure [34]. Finally, the European Prospective Investigation of Cancer (EPIC)-Norfolk Prospective Study examined the link between fruit and vegetable intake and plasma levels of vitamin C and risk of T2DM. During 12-year follow-up, 735 incident cases of diabetes were identified among nearly 21,000 participants [44]. A significant inverse association was found between plasma levels of vitamin C and risk of diabetes (OR=0.38, 95% CI=0.28-0.52). In the same study, a similar association was observed between fruit and vegetable intake and T2DM risk (OR=0.78, 95% CI=0.60-1.00) [44].

Despite epidemiologic findings generally pointing towards an association between increased vitamin C and reduced oxidation and inflammation, intervention trials assessing the effect of vitamin C supplementation on various markers of T2DM have yielded inconsistent results. One randomized, cross-over, double-blind intervention trial reported no improvement in fasting plasma glucose and no significant differences in levels of CRP, IL-6, IL-1 receptor agonist or oxidized LDL after supplementation with 3000 mg/day of vitamin C for 2 weeks in a group of 20 T2DM patients, compared to baseline levels [45]. Chen and colleagues performed a randomized, controlled, double-blind intervention on a group of 32 diabetic subjects with inadequate levels of vitamin C and found no significant changes in either fasting glucose or fasting insulin after intake of 800 mg/day of vitamin C for 4 weeks [46].

On the other hand, Wang and colleagues showed that the red blood cell sorbitol/plasma glucose ratio was reduced after supplementation with 1000 mg/day vitamin C for 2 weeks in a group of eight diabetics, although no differences were found in fasting plasma glucose [47]. Since sorbitol is a product of the pro-oxidative polyol pathway, this observation may suggest an inhibition of the polyol pathway by vitamin C among subjects with diabetes. Another study has shown that daily intake of ascorbic acid at 2000 mg/day improved fasting plasma glucose, HbA1c, cholesterol levels and triglycerides in 56 diabetics [48]. In agreement, Paolisso *et. al.* found that 1000 mg/day of vitamin C for 4 months improved LDL and total cholesterol, fasting plasma insulin and free radicals, although it did not affect triglycerides or HDL levels in a group of 40 diabetics [49].

Overall, it remains unclear whether vitamin C intake has an effect on factors related to T2DM. Although the epidemiologic evidence suggests that vitamin C, whether as a supplement or as part of a diet rich in fruits and vegetables, beneficially affects inflammatory markers and disease risk, the results of intervention trials in T2DM are conflicting. Small sample sizes, genetic variation, short intervention duration, insufficient dosage and disease status of the assessed cohorts may account for the lack of effect and the inconsistent outcomes observed in intervention studies. However, it is possible also that the status of vitamin C deficiency is a result of the oxidative and pro-inflammatory challenges associated with T2DM rather than a determinant of disease pathogenesis. Therefore, further research and long-term prospective studies are needed to elucidate the role of vitamin C as a modulator of inflammation and T2DM risk, and to evaluate its potential role as a preventive agent at a population level.

## 4. Vitamin E

Vitamin E encompasses a group of 8 compounds, including α, β, γ, and δ tocopherols and α, β, γ, and δ tocotrienols, with differing biological activities. Each compound contains a hydroxyl-containing chromanol ring with a varying number and position of methyl groups between the α, β, γ, and δ forms [29]. It is known to have a significant impact on improving a variety of immune functions [50]. Supplementation with vitamin E increases the rate of lymphocyte proliferation by enhancing the ability of T cells to undergo cell division cycles [51]. The effective anti-inflammatory action of vitamin E was substantiated from observations such as the increased expression of the *IL-2* gene and IL-1 receptor antagonist and the decreased expression of IL-4 following vitamin E supplementation in animal models [50]. Furthermore, vitamin E reduced the serum levels of inflammatory factors such as IL-1β, IL-6, TNF-α , PAI-1, and CRP in T2DM patients [52, 53]. Furthermore, vitamin E downregulates NFκB [52], the principal mediator of inflammatory signaling cascade and its potent lipophilic antioxidant effect on internal and external cell membranes as well as plasma lipoproteins, notably LDL. Based on this latter characteristic, studies in both animal models and humans have demonstrated that vitamin E intake blocks LDL lipid peroxidation, prevents the oxidative stress linked to T2DM-associated abnormal metabolic patterns [hyperglycemia, dyslipidemia, and elevated levels of FFAs], and, subsequently, attenuates cytokine gene expression [50, 52, 56, 57]. Despite these findings, a recent study evaluated the effects of a combination of vitamin C (1000 mg/day) and vitamin E (400 IU/day) for four weeks on insulin sensitivity in untrained and trained healthy young men and concluded that such supplementation may preclude the exercise-induced amelioration of insulin resistance in humans [58]. This may relate to the source of vitamin E used, i.e., α-, β-, γ-, or δ-tocopherol [59].

Overall, the immunomodulatory, anti-inflammatory and anti-oxidative functions of vitamin E strongly support its possible application in designing effective prevention and/or treatment protocols for T2DM [25, 56]. Current practices for diabetes prevention in the general population include lifestyle change, dietary intervention and exercise. Vitamin E supplementation may further aid in T2DM prevention and control through its anti-oxidant, anti-inflammatory and immunomodulatory properties. It seems reasonable, therefore, to suggest supplementation with vitamin E together with lifestyle change may be combined into a single program to enhance the success and effectiveness of intervention. This strategy could be more efficient in reducing the low-grade inflammation associated with pre-clinical T2DM and, subsequently the disease burden, than when a single approach is considered. Moreover, such a combined strategy can be introduced in general practice settings and in a population-based fashion with low expenditure and minimal side effects.

## 5. Vitamin D

The role of vitamin D in calcium and phosphorus homeostasis and bone metabolism is well understood. However, more recently vitamin D and calcium homeostasis have also been linked to a number of conditions, such as neuromuscular function, cancer, and a wide range of chronic diseases, including autoimmune diseases, atherosclerosis, obesity, cardiovascular

diseases, diabetes and associated conditions such as the metabolic syndrome and insulin resistance [25, 60-63]. In T2DM, the role of vitamin D was suggested from the presence of vitamin D receptors (VDR) in the pancreatic β-islet cells [63]. In these cells, the biologically active metabolite of vitamin D (*i.e.,* 1,25-dihydroxy-vitamin D; 1,25[OH]D) [64] enhances insulin production and secretion *via* its action on the VDR [63]. Indeed, the presence of vitamin D binding protein (DBP), a major predictor of serum levels of 25(OH)D and response to vitamin D supplementation [65, 66], and VDR initiated several studies demonstrating a relationship between single nucleotide polymorphisms (SNPs) in the genes regulating *VDR* and *DBP* and glucose intolerance and insulin secretion [67-69]. This further supports a role for vitamin D in T2DM and may explain the reduced overall risk of the disease in subjects who ingest >800 IU/d of vitamin D [61,70]. However, an alternative, and perhaps related, explanation was recently proposed for the role of vitamin D in T2DM prevention based on its potent immunomodulatory functions [71-73]. 1,25(OH)D modulates the production of the immunostimulatory IL-12 and the immunosuppressive IL-10 [74] and VDRs are present in most types of immune cells [75]. In this respect, supplementation with vitamin D [76] or its bioactive form, 1,25(OH)D [64], improved insulin sensitivity by preventing the excessive synthesis of inflammatory cytokines. This effect of vitamin D on cytokine synthesis is due to its interaction with vitamin D response elements (VDRE) present in the promoter region of cytokine-encoding genes. This interaction downregulates the transcriptional activities of cytokine genes and attenuates the synthesis of the corresponding proteins [76]. Vitamin D also deactivates NFκB, which transcriptionally upregulates the pro-inflammatory cytokine-encoding genes [77]. Downregulating the expression of NFκB and downstream cytokine genes inhibits β-cell apoptosis and promotes their survival [76].

As reviewed by Pittas et al [78], a number of cross-sectional studies in both healthy and diabetic cohorts have shown an inverse association between serum 25(OH)D and glycemic status measures such as fasting plasma glucose, oral glucose tolerance tests, hemoglobin A1c (HbA1c), and insulin resistance as measured by the homeostatic model assessment (HOMA-R), as well as the metabolic syndrome [79-84]. For example, data from the National Health and Nutrition Examination Survey (NHANES) showed an inverse, dose-dependent association between serum 25(OH)D and diabetes prevalence in non-Hispanic whites and Mexican Americans, but not in non-Hispanic blacks [81,84]. The same inverse trend was observed between serum 25(OH)D and insulin resistance as measured by HOMA-R, but there was no correlation between serum levels of vitamin D and β-cell function, as measured by HOMA-β [81,84]. Data from the same cohort also showed an inverse association between 25(OH)D and prevalence of the metabolic syndrome [81].

In prospective studies, dietary vitamin D intake has been associated with incidence of T2DM. For example, data from the Women's Health Study showed that, among middle-aged and older women, taking >511 IU/day of vitamin D reduced the risk of developing T2DM, as compared to ingesting 159 IU/day [85]. Furthermore, data from the Nurses Health Study also found a significant inverse correlation between total vitamin D intake and T2DM risk, even after adjusting for BMI, age, and non-dietary covariates [70]. Intervention studies have shown conflicting results about the effect of vitamin D on T2DM incidence. One study reported that supplementation with $1,25[OH]_2D_3$ for 1 week did not affect fasting glucose or

insulin sensitivity in 18 young healthy men [86]. Another study found that, among 14 T2DM patients, supplementing with 80 IU/day of 1 $\alpha$-$OHD_3$ ameliorated insulin secretion but did not improve glucose tolerance after a 75 g oral load [87]. Yet another study showed that, among 65 middle-aged men who had IGT or mild T2DM and adequate serum vitamin D levels at baseline, supplementation with 30 IU/day of 1-$\alpha$-$OHD_3$ for 3 months affected neither fasting nor stimulated glucose tolerance [88]. However, in a cross-over design, 20 diabetics with inadequate vitamin D serum levels who were given 40 IU/day of 1,25-OHD for 4 days had improved insulin secretion, but showed no changes in fasting or stimulated glucose or insulin concentrations [89]. Although the short duration of this cross-over trial may account for the lack of a significant overall effect, the results suggest that improving vitamin D status can modulate factors associated with the development and progression of T2DM.

The data from a 2-year-long trial designed to assess the effects of vitamin $D_3$ or 1-$\alpha$-$OHD_3$ supplementation on bone health in non-diabetic postmenopausal women were analyzed *a posteriori* and found no significant effect on fasting glucose levels [90]. A *post-hoc* analysis of data from a 3-year trial for bone health showed that daily supplementation with 700 IU of vitamin $D_3$ and 500 mg of calcium citrate malate did not change blood glucose levels or insulin resistance in elderly adults with normal glucose tolerance. These measures, however, were significantly improved in subjects with IGT at baseline [91]. In this trial the effect of fasting glucose levels in the high-risk group (*i.e.*, IGT) was similar to that observed in the Diabetes Prevention Program after an intensive lifestyle intervention or metformin treatment [92]. Taken together, the available information warrants exploring the possibility that vitamin D (alone or in combination with calcium) can be employed in developing population-based strategies for T2DM prevention and control.

## 6. β-carotene and lycopene

As previously stated, oxidative stress is involved in the development and complications of T2DM [60]. Patients with T2DM exhibit a reduced antioxidative defence, which negatively correlates with glucose levels and duration of the disease [93]. In diabetic subjects, the lack of metabolic homeostasis, the increased plasma ROS generation and the decreased efficiency of inhibitory and scavenger systems [60], all can that result in a status of oxidative stress that can have an etiological role in T2DM complications, e.g., retinopathy, chronic kidney disease, and cardiovascular diseases [94]. The synthesis of ROS was proposed to be primarily due to hyperglycaemia [95] resulting in stimulation of the polyol pathway, formation of advanced glycosylation endproducts, and subsequent formation of ROS. Hyperinsulinaemia, insulin resistance and inflammation, may all play a role in the synthesis of ROS in pre-diabetic and diabetic patients [60].

As we reviewed recently, the risk of T2DM can be mitigated by increased antioxidants intake [60]. Intake of $\alpha$- and β-carotene and lycopene has been shown to improve glucose metabolism in subjects at high risk of T2DM [96], and glucose metabolism has been associated with oxidative stress [95]. Indeed, diabetic patients have shown a predominantly elevated levels of lipid peroxidation ($F_2$-isoprostanes) [97]. *In vivo* lipid peroxidation, measured as $F_2$-isoprostanes, apprears to be influenced by the consumption of dietary

components such as antioxidants. It is therefore critical to examine the dietary effects of $\alpha$- and β-carotene and lycopeneon lipid peroxidation in patients with T2DM. The relationship between plasma levels of antioxidants and markers of oxidative stress and inflammation have been described in healthy population [58,98] and is yet to be identified in diabetic subjects. This will allow us to better define the role of $\alpha$- and β-carotene and lycopene in attenuating inflammation and modulating the oxidative stress during the course of T2DM development and progression.

## 7. T2DM complications: Cardiometabolic disease

It is well-established that T2DM is a risk factor for cardiometabolic diseases. Studies from our group demonstrated a relationship between T2DM and its risk factors and cardiometabolic disease markers [98,99]. We observed an apparent profile of metabolic phenotypes and inflammatory biomarkers, known to be related to the cardiometabolic disease risk, that emerges with the susceptibility to T2DM. These findings allowed us to establish a composite metabolic trait that lead to the development of improved strategies for early risk prediction and intervention.

In the same study population, we further demonstrated an association between plasma vitamin D level and T2DM risk, e.g., insulin resistance [100]. We found that the likelihood that T2DM develops and results in related complications is further increased as plasma vitamin D levels decrease. These studies highlights the possibility that micronutrient supplementation can be employed in the prevention of various T2Dm complications including cardimetabolic diseases. Moreover, there is a need to develop adequately powered randomized controlled clinical trials to evaluate the value of replenishment of vitamin D on T2DM and the related conditions, e.g., obesity, insulin resistance and cardiovascular diseases, as an approach for an effective population based strategy for disease prevention.

## 8. Public health prespectives

Introducing novel and effective prevention strategies in a public health setting necessitates considering approaches with the least [if any] side effects and the maximal preventive efficacy and outcome. Furthermore, the heterogeneity of the general Western population in terms of culture, location and resources renders creating a unified intervention program a formidable endeavour. In this context, applying nutritional intervention as an approach to attenuate inflammation and oxidative stress would be a feasible public health strategy for the T2DM. A conceptual model need to be implemented to improve the availability and accessibility of nutritious food as a factor that can be integrated into a comprehensive public health intervention strategy aimed at T2DM prevention.

Combining micronutrients supplementation or encouraging the consumption of nutritious diet should be explored in pre-diabetic subjects and the outcome should be compared to the effect(s) of changing current practices, such as lifestyle change, dietary intervention and exercise. The effectiveness of lifestyle-change intervention programmes for pre-diabetes also shows a promising effect on the reduction of overall incidence of T2DM or its complications,

and it can be implemented in general clinical practice [95]. A lifestyle-change programme including increased exercise and diet change (either by reduction in glycemic load or reduced-fat diet) demonstrated a significant difference between control and intervention groups in markers for risk of progression to T2DM including weight, BMI, and waist circumference [101]. In general, current approaches for the prevention of T2DM have been shown to be effective in delaying or preventing the progression from pre-diabetes to diabetes [102]. In patients with insulin resistance, these practices are known to improve insulin sensitivity and the overall predisposition to T2DM [103]. On the other hand, increasing intake of vitamin D to greater than 800 IU daily along with 1200 mg of calcium was reported to reduce the risk of developing T2DM by 33% [78]. In agreement, healthy older adults with impaired fasting glucose showed significant improvement in attenuating the glycemic response and insulin resistance when they increased the vitamin D to 700 IU/d and calcium to 500 mg/d for 3 yrs [70]. It seems reasonable, therefore, to suggest that the two preventive approaches for T2DM, *i.e.*, micronutrient supplementation and lifestyle change, may be combined into a single successful intervention programme. This strategy may be more efficient in reducing the burden of the disease in the general population and in vulnerable subpopulations than when a single approach is proposed. Moreover, such a combined approach may be introduced into the general practice setting and to the general population with low expenditure and minimal side effects [25,60].

Overall, the current state of knowledge warrants further study into the extent to which micronutrients can modify the association between markers of inflammation and oxidative stress and early stages of T2DM. There is evidence supporting the idea that vitamin supplementation can modify the genotype-phenotype association within the innate immune response (*i.e.*, the pro-inflammatory and inflammatory markers), and that it has an ameliorating effect on oxidative stress and the subsequent inflammatory signalling. This proposition may provide the mechanism by which nutritional factors prevent or delay disease development and can be introduced into the general population, as well as susceptible subpopulations. In relation to the current preventive approaches for T2DM, *e.g.*, lifestyle changes, exercise, and dietary intervention, exploring the efficacy of micronutrient supplementation on attenuating oxidative stress, the innate immune response and the ensuing inflammation and evaluating the outcome of this strategy on T2DM incidence may be assessed through a series of prospective population-based studies, first, to determine the feasibility and effectiveness of this protocol; second, to validate and evaluate this strategy and ensure replication of results; and, third, to monitor the outcome to quantify the overall preventive response in comparison with the current approaches.

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