Dietary total antioxidant capacity as a tool in health outcomes in middle-aged and older adults: a systematic review

Mary Anne Nascimento-Souza[1,*], Pedro Gontijo Paiva[2], Hércia Stampini Duarte Martino[3], Andréia Queiroz Ribeiro[4],

[1]Universidade Federal de Vicosa, Departament of nutrition and health, Vicosa, 36570-000 Brazil

[2]Universidade Federal de Minas Gerais, Belo Horizonte, 31270-901 Brazil Email: paivapg@gmail.com

[3]Universidade Federal de Vicosa, Nutrição e Saúde, Campus Universitário, Vicosa, 36570-000 Brazil Email: hercia72@gmail.com Email: andreiaribeiro@hotmail.com

[4]Universidade Federal de Vicosa, Vicosa, 36570-000 Brazil

[*](Corresponding Author) Email: maryannemoc@yahoo.com.br

ABSTRACT

The dietary total antioxidant capacity (TAC) has been a useful tool in epidemiological studies. To assess whether the TAC is associated with chronic diseases in middle-aged and older adults carried out a systematic review of articles indexed in MEDLINE and Science Direct. Of the 104 articles found, nine were included to meet the inclusion criteria. There was variation among the items on the sample size, sample origin, use of statistical tests, analysis of different outcomes and the use of assays to evaluate the TAC, which brought limitations to the comparability of results on the association of TAC with the outcomes of interest. However, in six studies we found an

inverse association between TAC and the risk of chronic diseases, showing that this method has great potential for clinical applications and public health.

Keywords

Total antioxidant capacity. Antioxidant. Chronic Disease. Aging. Elderly nutrition.

INTRODUCTION

A condition inherent to the aging process is the increase in oxidative stress and reduced antioxidant defense system (Indo et al., 2015). In this context, oxidative reactions can produce varying degrees of cell injury that play a role in the pathogenesis of acute neurological disorders and chronic non-communicable diseases, such as atherosclerosis, cardiovascular disease, neurodegeneration and cancer (Rani et al., 2016).

One way to neutralize or reduce this process in aging is to have an adequate diet in terms of nutrients and bioactive compounds with antioxidant capacity. In the study of antioxidants from the diet and its effects on health, a commonly used parameter is the dietary total antioxidant capacity (TAC) that considers all the antioxidants present in the diet and the synergistic effects between them (Pellegrini et al, 2003). Cooperation between the different antioxidants provides greater protection against reactive species than any isolated compound (Ghiselli et al., 2000; Serafini & Del Rio 2004).

Several assays are available to measure the antioxidants in foods. Ferric reducing antioxidant power (FRAP), total radical-trapping antioxidant parameter (TRAP), oxygen radical absorbance capacity (ORAC) and trolox equivalent antioxidant capacity (TEAC) are the most commonly used.

Diet can play a key role in regulating plasma redox state as the main external contributor of defense against reactive oxygen and nitrogen species (Serafini & Del Rio 2004). Thus, this review was conducted in order to answer if TAC is associated with health outcomes in middle-aged and older adults.

METHODOLOGY

This is a systematic review of the literature based on the analysis of articles about TAC and its association with health outcomes in middle-aged and older adults, conducted using the methodology preferred reporting items for systematic reviews and meta-analyses (PRISMA) (Moher et al., 2009).

To identify articles on the subject a search was carried out using the databases medical literature analysis and retrieval system online (MEDLINE) and Science Direct, between January and March 2016. We used the following terms in English and in quotes: "Total dietary antioxidant capacity", "Dietary total antioxidant capacity" and "Non enzymatic antioxidant capacity". The search was conducted by independent researchers. In order to locate studies not found in the initial search, a reverse search was carried out using the reference lists in the articles that were found.

For the inclusion of the articles, the following criteria were employed: the search terms were present in the title or abstract, observational studies, original studies, with health outcomes, carried out with healthy adults and older people from the community, with no date or language limits and with the articles available in full. We excluded articles with middle-aged adults and elderly people with any pathology, review articles, research reports, theses, dissertations, book chapters, books, expert opinion articles and those unrelated to the subject of the review.

After searching the databases and applying the search strategies, studies that showed duplicity between databases were identified. All resulting abstracts were read. In cases where reading the

abstract was not enough to establish whether the article should be included or not, considering the inclusion criteria, the article was read in its entirety to determine eligibility. When the abstract was enough, the articles were selected and then the full version was obtained to confirm eligibility and subsequent inclusion in the study. In case of disagreement between the evaluators an analysis and discussion of the article in question was carried out until there was consensus. A descriptive analysis of the chosen articles was performed. The review process was completed in March 2016.

RESULTS

After eliminating 26 duplicates, 205 articles were selected. One hundred ninety nine of these were excluded after reviewing the titles and abstracts. Of the seven eligible articles, three were excluded for the following reasons: one was not found in full for reading, one did not refer to the population of middle-aged adults and/or elderly and one did not evaluate health outcomes.

Five studies were found through reverse search and, in the end, nine studies were included in this systematic review, one of which contained only elderly (Devore et al., 2010) and eight contained both middle-aged and older adults. Figure 1 shows the summary of the article selection process. Of the nine studies included in the review, eight were cohort studies with a mean follow-up time ranging from six to 18 years and one was cross-sectional, all the studies were published between 2010 and 2015. Most studies (seven) used only one assay to evaluate TAC and FRAP (n = 4) was the most widely used assay.

The sample size ranged from 2,694 (Okubo et al., 2014) to 47,339 (Mekary et al., 2010) individuals and the participants ranged from 40 to 83 years of age. With regards to the country of

origin of the studies, two were carried out in the Netherlands (Pantavos et al., 2015; Devore et al., 2013), two in the United States (Devore et al., 2010; Mekary et al., 2010), three in Sweden (Rautiainen et al., 2012a; Rautiainen et al., 2012b; Rautiainen et al., 2013), one in Italy (Del Rio et al., 2011) and one in England (Okubo et al., 2014). No Brazilian study was found. The most studied outcome was stroke. The characteristics of the selected studies are shown in Table 1.

DISCUSSION

The evidence that reactive oxygen and nitrogen species and oxidative damage are involved in various inflammatory and degenerative diseases lead to growing scientific interest in the relationship between TAC and different health outcomes, as the cooperation between the various antioxidants provides greater protection against the action of reactive species than individual compounds.

This review found a small number of studies on TAC assessment in middle-aged and older adults. There was variation among the articles on the sample size, sample origin, use of statistical tests, analysis of different outcomes and assay use, which lead to limitations on the assessment of the results of association of TAC and the outcomes of interest in the different studies. These methodological differences make it difficult to compare the results, as well as to establish evidence.

Due to the complexity of food composition, studying each individual antioxidant compound is expensive and inefficient, moreover, there are synergistic interactions between the antioxidant compounds in a food mixture. Thus, the analyzed studies considered TAC as a useful tool for

assessing antioxidant capacity, since it captures the effects of a wide variety of antioxidant nutrients available in foods and their possible interactions. Which means including known nutrients as well as those that have not been well characterized, such as flavonoids (Devore et al., 2013).

One factor that makes it difficult to compare studies that analyze the same outcome is the use of different assays to evaluate TAC. Three studies evaluating stroke found different results, having used the TEAC (Del Rio et al., 2011), FRAP (Devore et al., 2013) and ORAC (Rautiainen et al., 2013) assays.

The different assays used to estimate dietary antioxidant scores may have led to discrepancies in the findings, as antioxidant capacity was measured by different mechanisms. However previous studies have shown that antioxidant scores based on TEAC and FRAP can predict important health outcomes (Puchau et al., 2010; Detopoulou et al., 2010; Agudo et al., 2007).

Another important factor that may have contributed to the results of the above studies are the different ways of measuring the outcomes that were used, since there was no standardization between them for the diagnosis of stroke. Moreover, the lack of association between TAC and some outcomes in the analyzed studies can be a result of a disadvantage of this approach (Devore et al., 2013; Okubo et al., 2014) because the components that contribute to the *in vitro* antioxidant activity may be poorly absorbed *in vivo*, as the *in vivo* system is more complex and the bioavailability of antioxidants in foods is highly variable.

Still regarding the type of assay, the most frequent in the analyzed studies was FRAP. Literature shows that there is no great advantage in using either assay (Devore et al., 2013). A database with antioxidant capacity values is limited to a particular assay and is not comparable to another database that uses different TAC assay. As there is no "gold standard" for assessing TAC, it is difficult to determine the most relevant assay to measure the exposure of interest (Pellegrini et al., 2003).

Several methods have been developed to measure TAC, they differ in their chemistry (generation of different radicals and/or target molecules) and in the way end points are measured (Pellegrini et al., 1999). The same food may have a different antioxidant capacity value depending on the applied method. Furthermore, even for antioxidant capacity values obtained using the same assay, a comparison between literature data shows great variability of the same food product which may be due to a lack of assay standardization or the different mechanisms involved (Pellegrini et al., 2003).

None of the studies included in this review analyzed the association between plasmatic TAC and the outcomes of interest. On the other hand, three studies (Rautiainen et al, 2012a; Rautiainen et al, 2012b; Rautiainen et al, 2013) used plasmatic TAC as a biomarker to assess the validity of the TAC estimates based on a FFQ which was designed exclusively to evaluate TAC. However, the correlation between TAC and plasmatic TAC evaluated by the ORAC assay was low (r = 0.31) (Rautiainen et al., 2008).

The plasmatic TAC measurements cannot provide an appropriate gold standard to TAC scores when they are based on long-term diet, which could justify the modest correlations presented by

the studies (Rautiainen et al, 2008; Pellegrini et al, 2007) between plasmatic TAC and TAC measurements. It should be noted that studies that evaluated plasmatic TAC immediately after the consumption of foods rich in antioxidants found a significant correlation between the two measurements (Maxwell et al., 1994; Serafini et al., 1994; Pedersen et al., 2000).

In epidemiological studies it is common that only one blood sample is taken and this may not reflect the consumption of antioxidants in the long term, being necessary to collect multiple samples so that the plasma can be considered as a biomarker of the antioxidant status. The plasma is subject to several influences such as antioxidant homeostatic control mechanisms, stress, environmental, pollution, inflammation and absorption (Rautiainen et al., 2008).

Thus, the evaluation of the antioxidant capacity may be an insufficient marker of antioxidant intake in the long term and the influence of factors other than the dietary intake in the values of antioxidant biomarkers may partially explain the poor correlation coefficients. It should be noted that these methods are based on chemical reactions *in vitro* and have no similarity to biological systems. Therefore, the results should be viewed with caution, as they do not measure bioavailability, *in vivo* stability, antioxidant retention in the tissues, or reactivity *in situ* (Wayner et al., 1985).

In vitro studies can only rank the antioxidant activity for a particular system reaction (FRAP, ORAC, TEAC, etc), while the *in vivo* effects remain uncertain. Furthermore, *in vivo*, the Nrf2 system is considered a major cellular defense mechanisms against oxidative stress, witch activates antioxidant enzymes (GST, SOD) with the antioxidant response element (ARE) being mostly responsible for this activation. The production of these enzymes is influenced by

exogenous antioxidants which, together with the endogenous antioxidants, control the cellular redox homeostasis (Young-Sam, 2012; Yu et al., 2013), in addition, a variety of bioactive dietary compounds act to increase the activity of Nrf2 transcription (Stefanson & Bakovic, 2014). The lack of evaluation of indirect antioxidant mechanisms limits the measurement capacity of the TAC tool, since these act more potently inducing the synthesis of antioxidant enzymes.

It was found that the FFQ was the most used instrument to assess food intake, it should be noted that all studies used validated evaluation methods for assessing dietary intake. The FFQ evaluates the frequency of consumption, but not the exact amount (in grams) of food intake, which is a limitation due to individual variations in the portion sizes. Moreover, regarding the method used to gather dietary data, not all studies made it clear whether the information was collected by the interviewer or if the questionnaire was filled by the volunteer, which may lead to greater variability in consumption quantification, changing the studied associations.

The percentage of FFQ items with antioxidant capacity values assigned in the database varied greatly among the analyzed studies. Four studies did not report this information (Mekary et al., 2010; Del Rio et al., 2011; Devore et al., 2013; Pantavos et al., 2015) and in the others the percentage ranged from 44.8% (Obubo et al., 2014) to 100.0% (Devore et al., 2010). The absence of antioxidant capacity values for the FFQ items can lead to an underestimation of TAC and therefore influence the measures of association.

Two studies calculated TAC scores based on the contribution of supplements and foods (Devore et al., 2010; Mekary et al., 2010). In the study by Mekary et al., (2011) the use of vitamin C

supplement was the main contributor to the analysis of antioxidant capacity from foods and supplements.

In other studies TAC values could only be associated to food items and not to supplements with antioxidant properties. Associations of TAC from food with outcomes did not change significantly compared to TAC analysis taking supplements into account. Furthermore, these studies reported no coverage rate of antioxidant capacity values for supplements.

Regarding the analysis of food consumption in cohort studies, only two studies (Devore et al., 2010; Mekary et al., 2010) used the accumulated TAC on various dietary reports, which reduces random measurement errors (Hu et al., 1999). In other studies TAC intake was measured only at the baseline, and may not reflect accurately the long-term consumption patterns. Thus, one cannot rule out that the dietary TAC may have changed during follow-up.

The successful application of this tool is highly dependent on the integrity and validity of the food consumption data and the accuracy of food composition data. Errors in measurement instruments that are used to evaluate the dietary intake of antioxidants may contribute to underestimation of the studied associations.

Databases with TAC values developed in other countries may also lead to underestimation of TAC, attenuation or invalidity of the assessed association, since the antioxidant content may vary according to geographic location, growing conditions and processing of the analyzed food (Prior & Gu 2005). Among the studies analyzed, only two used TAC databases developed using local food items (Devore et al, 2010; Mekary et al., 2010).

The main foods that contributed to TAC in most studies were coffee, decaffeinated coffee and tea, but there was variation in the relative contribution of these products between the studies. Vegetables, fruits and whole grains had higher contribution to TAC in the studies by Rautiainen et al. (2012a; 2012b; 2013) that considered that the antioxidants in coffee and tea were poorly absorbed (Natella et al., 2002) and in the study by Okubo et al (2012b), which attributed this result to the limited number of available values of antioxidant capacity of foods for the ORAC assay when compared to other databases of the analyzed assays, particularly the lack of data for coffee.

There was a loss of information in the dietary data in the studies analyzed, only one study (Pantavos et al., 2015) used a feature to deal with these losses, such as multiple imputation, thus reducing potential bias associated with data loss. Also, only one study (Devore et al., 2010) evaluated the loss to see it was selective. For the other studies, one cannot rule out the possibility of selection bias, which may also help to explain the differences in results observed between them.

An advantage of the TAC tool is the fact that individual antioxidants are not associated with the overall risk of the outcomes. In this sense TAC evaluates the contribution of antioxidants in the diet as a whole, rather than assessing the individual effects (Pantavos et al., 2015; Rautiainen et al., 2013). On the other hand, some authors criticize the strategy of classifying foods for its antioxidant capacity, because of the fact that TAC is an *in vitro* parameter, which does not consider all the bioavailability issues related to most antioxidant compounds introduced with a varied diet (Fraga et al., 2014; Pompella et al., 2014).

However, although antioxidant activity is only one of many mechanisms that benefit health through which the foods listed with a high TAC contribute to a healthy diet, TAC evaluation can still be considered a good tool that help in the choice of foods and beverages in the context of a healthy diet.

CONCLUSION

The results show that despite its limitations, TAC has a great potential for clinical and public health applications, and in studies with middle-aged adults and the elderly, as it provides the sum of the protective activity of antioxidants in the diet. In addition, TAC scores were demonstrated to predict important outcomes related to health in the analyzed group. It is necessary to carry out intervention studies to increase the evidence of the effects of total antioxidant capacity in health, since oxidative damage is linked to a number of health outcomes in middle-aged and older adults.

The estimation of dietary antioxidant capacity provides additional information because it identifies and classifies the potential sources of antioxidants in complex diets, which allows classifying diets as well as individuals in relation to the intake of antioxidants. Therefore TAC is shown to be a useful tool. In this sense, it is believed that TAC can be a useful tool in nutritional epidemiology studies and in the planning of actions to promote better nutrition among middle-aged adults and elderly. Such actions may include, for example, the implementation of dietary antioxidant interventions in order to contribute in changing eating habits and lifestyle.

ACKNOWLEDGMENTS

The authors also express their gratitude for financial support from National Counsel of Technological and Scientific Development (CNPq) (grant number 160287/2014-6).

REFERENCES

Agudo, A., Cabrera, L., Amiano, P., et al. (2007). Fruit and vegetable intakes, dietary antioxidant nutrients, and total mortality in Spanish adults: findings from the Spanish cohort of the European Prospective Investigation into Cancer and Nutrition (EPIC-Spain). *Am J Clin Nutr*. 85: 1634-42.

Del Rio, D., Agnol,i C., Pellegrini, N., et al. (2011). Total antioxidant capacity of the diet is associated with lower risk of ischemic stroke in a large Italian cohort. *J Nutr.* 14: 118-23.

Detopoulou, P., Panagiotakos, D. B., Chrysohoou, C., et al. (2010). Dietary antioxidant capacity and concentration of adiponectin in apparently healthy adults: the ATTICA study. *Eur J Clin Nutr.* 64: 161-8.

Devore, E. E., Feskens, E., Ikram, M. A., et al. (2013). Total antioxidant capacity of the diet and major neurologic outcomes in older adults. *Neurology*. 80:904-10.

Devore, E. E., Kang, J. H., Stampfer, M. J., et al. (2010). Total antioxidant capacity of diet in relation to cognitive function and decline. *Am J Clin Nutr*. 92: 1157-64.

Fraga, C. G., Oteiza, P.I., Galleano, M. (2014). In vitro measurements and interpretation of total antioxidant capacity. *Biochim Biophys Acta*. 1840: 931-4.

Ghiselli, A., Serafini, M., Natella, F., et al. (2000). Total antioxidant capacity as a tool to assess redox status: critical view and experimental data. *Free Radic Biol Med*. 29: 1106-14.

Hermsdorff, H. H., Puchau, B., Volp, A.C., et al. (2011). Dietary total antioxidant capacity is inversely related to central adiposity as well as to metabolic and oxidative stress markers in healthy young adults. *Nutr Metab (Lond)*. 8:59.

Hu, F.B., Stampfer, M.J., Rimm, E., et al. (1999). Dietary fat and coronary heart disease: a comparison of approaches for adjusting for total energy intake and modeling repeated dietary measurements. *Am J Epidemiol.*149:531-40.

Indo, H.P., Yen H.C., Nakanishi I., et al. (2015). A mitochondrial superoxide theory for oxidative stress diseases and aging. *J Clin Biochem Nutr.* 56:1-7.

Maxwell, S., Cruickshank, A., Thorpe, G. (1994). Red wine and antioxidant activity in serum. *Lancet.* 344: 193-4.

Mekary, R. A., Wu, K., Giovannucci, E., et al. (2010). Total antioxidant capacity intake and colorectal cancer risk in the Health Professionals Follow-up Study. *Cancer Causes Control*. 21:1315-21.

Moher, D., Liberati, A., Tetzlaff, J., et al. (2009). PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Ann Intern Med*.151(4): 264-9.

Natella, F., Nardini, M., Giannetti, I., et al. (2002). Coffee drinking influences plasma antioxidant capacity in humans. *J Agric Food Chem.* 50: 6211-6.

Okubo, H., Syddall, H. E., Phillips, D. I., et al. (2014). Dietary total antioxidant capacity is related to glucose tolerance in older people: the Hertfordshire Cohort Study. *Nutr Metab Cardiovasc Dis*. 24:301-8.

Pantavos, A., Ruiter, R,. Feskens, E. F., et al. (2015). Total dietary antioxidant capacity, individual antioxidant intake and breast cancer risk: the Rotterdam Study. *Int J Cancer*. 136: 2178-86.

Pedersen, C. B., Kyle, J., Jenkinson, A. M., et al. (2000). Effects of blueberry and cranberry juice consumption on the plasma antioxidant capacity of healthy female volunteers. *Eur J Clin Nutr*. 54: 405-8.

Pellegrini, N., Ke, R., Yang, M., et al. (1999). Screening of dietary carotenoids and carotenoid-rich fruit extracts for antioxidant activities applying the 2, 2′-azobis (3-ethylenebenzothiazoline-6-sulfonic) acid radical cation decolorization assay. *Methods Enzymol*. 299: 379-389.

Pellegrini, N., Salvatore, S., Valtueña, S., et al.. (2007). Development and validation of a food frequency questionnaire for the assessment of dietary total antioxidant capacity. *J Nutr*. 137: 93-8.

Pellegrini, N., Serafini, M., Colombi, B., et al. (2003). Total antioxidant capacity of plant foods, beverages and oils consumed in Italy assessed by three different in vitro assays. *J Nutr*. 133: 2812-9.

Pompella, A., Sies, H., Wacker, R., et al. (2014). The use of total antioxidant capacity as surrogate marker for food quality and its effect on health is to be discouraged. *Nutrition.* 30: 791-3.

Prior, R. L., Gu, L. (2005). Occurrence and biological significance of proanthocyanidins in the American diet. *Phytochemistry*. 66: 2264-80.

Puchau, B., Zulet, M. A., de Echávarri, A.G., et al. (2010). Dietary total antioxidant capacity is negatively associated with some metabolic syndrome features in healthy young adults. *Nutrition.* 26: 534-41.

Rani, V., Deep, G., Singh, R.K., et al. (2016).Oxidative stress and metabolic disorders: Pathogenesis and therapeutic strategies. *Life Sci.* 148: 183-93.

Rautiainen, S,. Levitan, E. B., Mittleman, M. A., et al (2013). Total antioxidant capacity of diet and risk of heart failure: a population-based prospective cohort of women. *Am J Med*. 126: 494-500.

Rautiainen, S., Larsson, S., Virtamo, J., et al. (2012b). Total antioxidant capacity of diet and risk of stroke: a population-based prospective cohort of women. *Stroke*. 43:335-40.

Rautiainen, S., Levitan, E.B., Orsini, N., et al. (2012a). Total antioxidant capacity from diet and risk of myocardial infarction: a prospective cohort of women. *Am J Med.* 125:974-80.

Rautiainen, S., Serafini, M., Morgenstern, R., et al. (2008). The validity and reproducibility of food-frequency questionnaire-based total antioxidant capacity estimates in Swedish women. *Am J Clin Nutr.*87: 1247-53.

Serafin,i M., Ghiselli, A., Ferro-Luzzi, A. (1994). Red wine, tea, and antioxidants. *Lancet*. 344: 626.

Serafini, M., Del Rio, D. (2004). Understanding the association between dietary antioxidants, redox status and disease: is the Total Antioxidant Capacity the right tool? *Redox Rep.* 9:145-52.

Stefanson, A.L., Bakovic, M. (2014). Dietary regulation of Keap1/Nrf2/ARE pathway: focus on plant-derived compounds and trace minerals. Nutrients. 19;6 (9):3777-801.

Wang, Y., Yang, M., Lee, S. G., et al. (2012). Dietary total antioxidant capacity is associated with diet and plasma antioxidant status in healthy young adults. *J Acad Nutr Diet*. 112:1626-35.

Wayner, D. D., Burton, G. W., Ingold, K.U., et al. (1985). Quantitative measurement of the total, peroxyl radical-trapping antioxidant capability of human blood plasma by controlled peroxidation. The important contribution made by plasma proteins. *FEBS Lett.* 187: 33-7.

Young-Sam, K. (2012). Regulation of Nrf2-Mediated Phase II Detoxification and Anti-oxidant Genes. *Biomol Ther (Seoul).* 20(2): 144--151.

Yu, M., Xu, M., Liu, Y. et al. (2013). Nrf2/ARE is the potential pathway to protect Sprague-Dawley rats against oxidative stress induced by quinocetone. *Regul Toxicol Pharmacol.* 66(3):279-85.

Table 1. Characteristics of the selected studies

Autor (year)/ Country	Design of the study	Sample size/ Sample source	Age (years)	Study Objective	Assay used/ Food intake evaluation tool	Outcome	Measurement of outcome	Confounding variable	Associations observed
Pantavos et al., (2014) Netherlands	Prospective cohort	3,209 women/ Rotterdam Study	>55	Assess association between dietary TAC and risk of breast cancer in postmenopausal women	FRAP SFFQ with 170 food items	Breast cancer	Through the general practitioners and by linkage with a nationwide registry of histo and cytopathology in the Netherlands	Age, BMI, educational level, family history of breast cancer, smoking status, alcohol consumption, household income, hormone use, reproductive history, dietary fat and fiber intake, comorbidities to baseline, hormone and multivitamin use	High dietary TAC score was associated with a lower risk of breast cancer

Okubo et al., (2014) England	Cross-sectional	1441 men and 1,253 women/ Hertfordshire Cohort Study	59-73	Assess association between dietary TAC and glucose tolerance	ORAC TEAC TRAP FRAP SFFQ with 134 food items	Markers of glucose metabolism	75-g oral glucose tolerance test	Age, BMI, smoking status, usage of dietary supplement, gender, energy intake, physical activity level	High dietary TAC score was associated with better glucose tolerance
Devore et al., (2013) Netherlands	Prospective cohort	5,395 men and women/ Rotterdam Study	> 55	Assess association between dietary TAC and dementia, stroke	FRAP SFFQ with 170 food items	Dementia and stroke	Dementia: Mini-Mental State Examination and Geriatric Mental State, evaluation by a neurologist or neuropsychologist Stroke: check medical records to verify self-reported strokes at baseline	Age, BMI, educational level, smoking status, supplement use, total calorie intake, APOE e4 genotype, high blood pressure, diabetes, myocardial infarction.	High dietary TAC score was not associated with lower risk of dementia and stroke

Rautiainen et al., (2013) Sweden	Prospective cohort	33,713 women/ Swedish Mammography Cohort	49-83	Assess association between dietary TAC and incidence of heart failure	ORAC SFFQ with 96 food items	Heart failure	Check Swedish Hospital Discharge Registry	Age, BMI, educational level, smoking status, alcohol consumption physical activity, hypertension, diabetes, family history of myocardial infarction, total energy intake, dietary supplement use, incident myocardial infarction	High dietary TAC score was with lower risk of heart failure

Rautiainen et al., (2012a) Sweden	Prospective cohort	32,561 women/ Swedish Mammography Cohort	49-83	Assess association between dietary TAC and myocardial infarction incidence	ORAC SFFQ with96 food items	Myocardial infarction	Check Swedish Hospital Discharge Registry	Age, BMI, smoking, alcohol consumption, energy intake, physical activity educational level, hormone replacement therapy use, aspirin use, hypertension, hypercholesterolemia, family history of myocardial infarction, and dietary supplement use, fruit and vegetable consumption, intakes of saturated fatty acids, monounsaturated fatty acids and polyunsaturated	High dietary TAC score was associated with lower of myocardial infarction

Rautiainen et al., (2012b) Sweden	Prospective cohort	31,035 women/ Swedish Mammography Cohort	49-83	Assess association between dietary TAC and stroke incidence	ORAC SFFQ with 96 food items	Stroke	Check Swedish Hospital Discharge Registry	Age, BMI, smoking, alcohol consumption, physical activity, educational level, hypertension, hypercholesterolemia, diabetes, family history of myocardial infarction before age 60 years, aspirin use, dietary supplement use, energy intake, coffee consumption, consumption of red meat and fish, fruit and vegetable consumption	Higher dietary TAC score was associated with lower risk of stroke

Del Rio et al., (2011) Italy	Prospective cohort	41,620 men and women/ Europeans Prospective Investigation into Cancer and Nutrition	44-61	Assess relation between dietary TAC and risk of ischemic and hemorrhagic stroke	TEAC SFFQ with 150 food items	Ischemic and hemorrhagic stroke	Hospital discharge diagnosis archives or/and after direct evaluation of medical notes and/or the information derived from the baseline questionnaire and death certificates	Hypertension, BMI, smoking status, education, level, nonalcohol energy intake, alcohol drinking, waist circumference, obesity, physical activity	Higher dietary TAC score was associated with lower risk ischemic stroke

Devore et al., (2010) United States	Cohort	16,010 women/ Nurses' Health Study	≥70	Assess association between dietary TAC and cognitive function and decline	FRAP SFFQ with 61 food itens and one expanded version with ≈130 items	Cognitive function and decline	Telephone Interview of Cognitive Status, East Boston Memory Test, category fluency, delayed recall of the TICS 10-word list and digit span backward	Age, education level, antidepressant use, smoking status, physical activity, BMI, high blood pressure, myocardial infarction, type 2 diabetes, vitamin E, C and multivitamin supplement use	Higher dietary TAC score was not associated with better cognitive health

Mekary et al., (2010) United States	Prospective cohort	47,339 men/ The Health Professionals Follow-up Study	40-75	Assess association between dietary TAC and colorectal cancer incidence	FRAP SFFQ with 131 food items	Colorectal cancer	Medical records	Age, BMI, alcohol intake, physical activity, aspirin use, family history of colorectal câncer, history of previous endoscopy, supplement use containing antioxidants, energy intake, red meat consumption, total calcium intake, dietary folate intake, dietary vitamin D intake, pack years of smoking before age 30, race	High dietary TAC score was not associated with lower risk of colorectal cancer

FRAP ferric-reducing ability of plasma; SFFQ semiquantitative food-frequency questionnaire; BMI body mass index; TAC total antioxidante capacity; ORAC,oxygen radical absorbance capacity; TEAC, trolox equivalent antioxidant capacity; TRAP total radical-trapping antioxidant parameter

Figure 1. Flowchart of studies selection