# Physical Activity does not Influence the Effect of Antioxidant Supplementation at Nutritional Doses on the Incidence of Impaired Fasting Glucose: A 7.5 Year Post-hoc Analysis from the SU.VI.MAX Study

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## Abstract

Supplementation with high doses of antioxidant vitamins prevents the insulin-sensitizing effects of physical exercise. However, little is known whether antioxidant supplementation affects the incidence of impaired fasting glucose (IFG). Data from 8938 subjects included in a randomized controlled trial on supplementation with antioxidants vitamins and trace elements at nutritional doses (SU.VI.MAX) were used to examine the effects of antioxidants on incident IFG after 7.5 years of follow-up, with and without stratification for daily physical exercise. The odds-ratio (95% CI) for developing an IFG among study participants receiving antioxidant supplementation was 1.34 (0.90–1.97) (p = 0.33), in comparison to placebo. This risk did not vary significantly according to physical activity level (p for homogeneity = 0.10). Supplementation with trace elements and antioxidants at nutritional doses apparently does not affect the incidence of IFG irrespective of self-reported physical exercise habits.

## Introduction

Antioxidants are widely used as dietary supplements. However, their putative protective effects on the risk of type 2 diabetes or intermediate metabolic disorders have rarely been studied. Findings from the SU.VI.MAX trial suggest that long-term antioxidant supplementation at nutritional doses does not affect either fasting plasma glucose (FPG) [1] or the risk for the metabolic syndrome [2]. A recent short-term trial suggests that supplementation with higher doses of antioxidants precludes the insulin-sensitizing effects of physical exercise in healthy young men [3]. Because these 2 studies differ in several regards (dosage, types of antioxidant supplements, study population, and physical activity assessment or level), we aimed to elucidate whether antioxidants at nutritional doses may have a diabetes-promoting effect depending on the regularity and/or intensity of physical exercise.

## Subjects and Methods

Data are from the SU.VI.MAX study, a randomized trial described elsewhere [4, 5]. A total of 13017 subjects were included in 1994–1995 for a mean (± standard deviation, SD) follow-up of 7.5 ± 0.3 years. Supplementation included either a combination of 120 mg vitamin C, 30 mg vitamin E, 6 mg β-carotene, 100 µg selenium, and 20 mg zinc, or a matching placebo.

The overall level of habitual physical activity was assessed at baseline using the following questions: "Do you have a regular physical activity (transportation, work, leisure): yes/no?" and "If yes, does it last for more than 1 h per day: yes/no?". Physical activity was coded in 3 categories: irregular, regular but < 1 h/day, regular and ≥ 1 h/day. Level of education was obtained from a questionnaire (primary school, high school, university or equivalent). Blood samples were obtained after an overnight 12-h fast, and all biochemical measurements were centralized in a single laboratory. Fasting blood glucose (FBG) was measured by using an enzymatic method (Advia 1650; Bayer Diagnostic, New York, NY, USA).

Post-hoc analyses were performed in subjects for whom baseline data – FPG, supplementation status (intervention or placebo), age, sex, and physical activity level – and data on FPG after 7.5 years of follow-up were available. For the current analysis, subjects who had a FPG ≥ 6.1 mmol/l and/or who reported the use of antidiabetic medication

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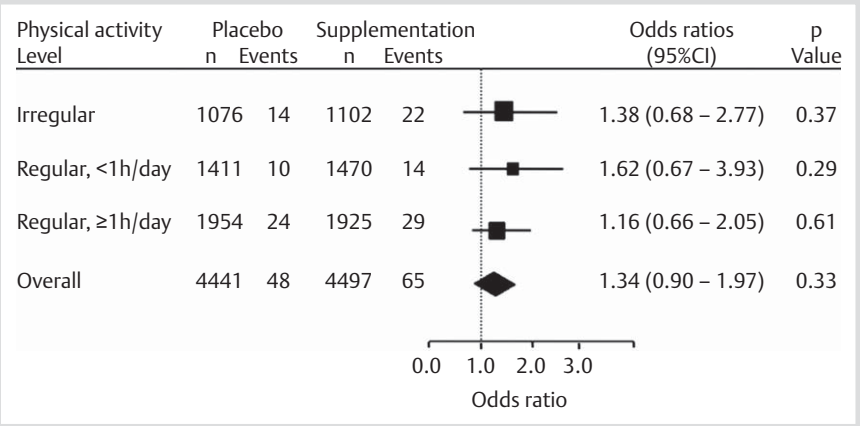


**Fig. 1** Risk (95 % confidence intervals) of 7.5 years incident impaired fasting glucose (IFG ≥6.1 mmol/l or treatment) in subjects supplemented by antioxidants in comparison to placebo by different physical activity levels in the SU.VI. MAX cohort (p for homogeneity = 0.10).

at baseline were excluded. The final sample included 8 938 subjects. Those with a FBG >6.1 mmol/l at follow-up and/or use of antidiabetic medication were classified as having incident impaired fasting glucose (IFG).

### Statistical analysis

Results are expressed as percentages or means (SD). Characteristics of the study participants according to placebo and intervention groups across physical activity levels were compared using analysis of co-variances. Logistic regression models were used to compute the odds-ratios and 95 % confidence intervals (OR, 95 % CI) of antioxidant supplementation on the 7.5 years incidence of IFG stratified by physical activity level, and a test of homogeneity was performed across physical activity levels. Also, to test the robustness of our results, generalized linear models were performed with fasting blood glucose as continuous variable, and an interaction term between treatment allocation group and physical activity level. All statistical analyses were carried out using standard procedures in SAS software (version 9.02; SAS Institute, Cary, NC). Statistical significance was set at $p < 0.05$ with 2-sided tests.

## Results

Mean age was 48.4 years (SD = 6.4). 33 % of study participants were men. None of the studied clinical and biological parameters varied across physical activity and supplementation group (age, sex, smoking status, educational level, body mass index, systolic and diastolic blood pressure, FPG, fasting plasma triglycerides, fasting plasma cholesterol, all $p > 0.27$).

Regular exercise for less than 1 h per day (n = 2 881) decreased the risk for IFG significantly, as follows: OR = 0.52 (95 % CI: 0.31–0.88), in comparison to individuals that reportedly exercised on an irregular basis (n = 2 178, reference group). Regular exercise for 1 h per day or more (n = 3 879) tended to decrease the risk for IFG: OR = 0.70 (95 % CI: 0.46–1.08), in comparison to the reference group. Further adjustment on energy intake did not modify the pattern of the associations (data not shown).

The risk of developing IFG among study participants under antioxidant supplementation, in comparison to those taking the placebo was: OR = 1.34 (0.90–1.97). This risk did not vary significantly according to physical activity level (p for homogeneity = 0.10, **Fig. 1**).

We furthermore tested whether there was an interaction between physical activity and antioxidant supplementation on fasting blood glucose by evaluating if the effect of physical activity on fasting blood glucose was different in the supplemented vs. the placebo group. Using fasting plasma glucose either as a continuous variable (data not shown), or as a categorical variable (data not shown) no significant differences were observed.

## Discussion and Conclusions

The current findings suggest that supplementation with antioxidants at nutritional doses does not significantly affect the risk for developing IFG. In particular, there is no interaction between the diabetes-preventive effects of physical exercise and antioxidant supplementation at nutritional doses, as used in the SU.VI. MAX Study. In apparent contrast, a recent intervention trial that used high doses of vitamin C (1 000 mg/day) and vitamin E (400 IU/day) has shown that the insulin-sensitizing effects of physical exercise are significantly impaired by antioxidant supplementation, suggesting that high-dose antioxidants may impair the diabetes-preventive effects of exercise [3]. When comparing these 2 trials, several differences should be noted. The SU.VI.MAX trial used a combination of low dosage of antioxidant and trace elements for 7.5 years, with self-reported physical activity and was population-based. It should be noted that self-reported physical activity levels bear the risk of significant estimation errors; moreover estimates were documented at initiation of the trial only, hence putative changes in physical activity after this date could not be considered in the statistical models. Moreover, the exercise-intervention trial used significantly higher doses of vitamins C and E only for 4 weeks and was restricted to young healthy men [3]. Hence, differences in methodology, the presence of trace elements, and the amounts of antioxidants used may help to explain differences in findings. We conclude that supplementation with trace elements and antioxidants at nutritional doses apparently does not affect the incidence of IFG irrespective of baseline and self-reported physical exercise habits.

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