







## The Effect of Synbiotic Supplementation on Total Antioxidant Capacity Levels in Adolescents Exposed to Air Pollution: A Randomized, Single-Blind, Controlled Clinical Trial

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### Abstract

**Background:** Exposure to air pollution might increase malondialdehyde (MDA) levels. Synbiotics by changing intestinal flora can decrease the inflammatory markers. There is lack of evidence about the effect of synbiotic supplementation on oxidative stress in children and adolescent. This study aims to evaluate the effect of synbiotic supplementation on MDA in healthy adolescents who were exposed to air pollution.

**Methods** This randomized single-blind, controlled trial was conducted among 70 participants aged 10-18 years who were exposed to air pollution. Participants were randomly divided into two groups that received either a synbiotic (n= 38) or omega-3 (n= 32) for 8 weeks. MDA was measured at baseline and after the intervention.

**Results:** MAD levels decreased significantly at the end of the intervention in comparison with baseline in synbiotic group ( $148.80 \pm 80.72$  vs  $51.54 \pm 82.94$ ,  $p < 0.001$ ). In crude model, no significant changes were demonstrated in MDA levels between groups ( $P = 0.75$ ). However, after adjustment the analysis with confounder significant reduction was observed with synbiotic consumption.

**Conclusion:** synbiotic supplementation might be associated with reduction of MDA levels that may be increased due to air pollution. Investigation the effects of air pollutants on children and adolescent is very important. Further large-scale studies are required to highlight the importance of synbiotic on adverse effects of air pollution in pediatric age groups.

### Keywords

Synbiotics, Dietary supplements, Air pollution, Malondialdehyde, Oxidative stress, Child

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## Introduction

One of the global public health emergencies is air pollution that the World Health Organisation (WHO) recognize it as a major environmental risk. There is growing evidence that exposure to air pollution has adverse impact on human health (1). Air pollutants, including airborne particulate matter increase oxidative stress in the human body. Oxidative stress is associated with the development of disease. Reactive oxygen species (ROS) modify DNA and lipids (2). Many studies showed that increased exposure to particulate matter is associated with increased levels of oxidized DNA and lipids (3, 4). One biomarker of oxidative stress is malondialdehyde (MDA) that is the most widely used lipid peroxidation technique. Increasing serum MDA levels reflects increased free radical production. It leads to impaired physiological processes and the onset of health disorders (3, 5).

Previous studies showed that supplementation with probiotics by changing intestinal and gastrointestinal flora can significantly decrease the inflammatory markers. Probiotics are live microorganisms and when administered in sufficient amount, can has health advantage to their host (6). Prebiotics are fermented ingredients that increase the gastrointestinal microbial. Synbiotic is a product that contains both probiotics and prebiotics. Some studies have reported the beneficial effects of prebiotics, probiotics and synbiotics on oxidative stress (7, 8). While others did not show any significant association (9, 10)

Exposure to air pollution might increase MDA levels. Various biomarkers were investigated to evaluate the relationship between air pollution exposure and oxidative stress. However, only a limited number of epidemiological studies assessed MDA as a biomarker of oxidative stress in relation to air pollution (2, 11). Investigation of the effects of air pollutants on children and adolescent is very important. There is lack of evidence about the effect of synbiotic supplementation on oxidative stress due to air pollution in children and adolescent. Therefore, this study aims to evaluate the effect

of synbiotic supplementation on MDA as marker of oxidative stress in healthy adolescents who were exposed to air pollution.

## Methods

### Participants

The current study was a randomized, single-blind, placebo-controlled clinical trial. At first, a total of 110 subjects aged 10 to 18 years that were exposed to air pollution in Isfahan city, Iran were enrolled in the study and finally 70 subjects (32 girls and 38 boys) completed the study (Figure 1). Subjects were randomly allocated to either a synbiotic group (n= 38) or omega-3 group (n= 32).

Inclusion criteria were healthy subject aged 10 to 18 years without any chronic disease, physiological disorders and endocrine diseases that were exposed to air pollution. Subjects should not take any antioxidant supplements, probiotic products or herbal products dietary supplements during the study and in the past month. Exclusion criteria were gastrointestinal problems or sensitivity to the supplements. Those participants with low compliance for following the study were excluded from the trial.

We assessed individuals' compliance with the intervention by counting the number of capsules remaining in each package (consuming at least 90% of the capsules delivered during the study). Subjects were checked weekly by phone interview.

Participants were randomly assigned based on the permuted block randomization method into two groups, synbiotic and omega-3. A table of random numbers was used for random allocation.

The sample size was determined using a formula for a parallel design randomized controlled trial in which type I and II error rates were considered 5% and 20% (statistical power of 80%) with an addition of 15% to cover up the possible drop outs, the sample size was determined as 50 participants in each group.

The study protocol was in accordance with the Declaration of Helsinki and were reviewed and approved by Research and Ethics council of

Isfahan University of Medical Sciences. Written informed consent and oral assent were obtained from parents and participants, respectively. This trial was registered as IRCT20170501033747N3.

#### **Supplement administration:**

Participants were allocated to synbiotic and omega-3 groups. Statistics specialist would be blind to the treatment groups until the statistical analysis be completed. All subjects were asked not to consume probiotic products for two weeks before entering the study.

The synbiotic group received two FamiLact capsules (Zist takhmir company, Tehran, Iran). FamiLact® is a synbiotic (probiotic + prebiotic) formulation and contains high amounts of nine safe and beneficial bacterial strains plus fructooligosaccharides as prebiotic. Strains and prebiotic in FamiLact capsule are *Lactobacillus rhamnosus*, *Lactobacillus casei*, *Lactobacillus bulgaricus*, *Lactobacillus acidophilus*, *Bifidobacterium breve*, *Bifidobacterium longum*, *Streptococcus thermophiles*. Another group received 1000 mg omega-3 capsule (zahravi pharmaceutical company, Tabriz, Iran) daily. Participants in each group received supplements for eight weeks. One message was sent daily for consuming capsules and increase compliance. Due to ethical issues and because all participants were exposed to air pollution, one group received omega-3 because previous studies have shown beneficial effects of omega-3 on air pollution (12-14).

#### **Air pollution assessment:**

Data of air pollution measurement stations were recorded daily for the 7 days before taking blood samples from the participants. The mean values of seven 24-hour means of air quality index (AQI) was considered. Among the air pollution measurement stations, one station was selected randomly. From the schools that were located near that station, two of them are selected, and then 100 students who were eligible for the study were invited to participate by random selection.

Consumption of capsules was started at the same time for all participants, to be uniform in terms of exposure to air pollution.

#### **Malondialdehyde (MDA) assessment**

The serum MDA level was measured in duplicate using an enzyme-linked immunosorbent assay (ELISA) kits (EASTBIOPHARM Company). The sensitivity of kit was 0.22 nmol/ml. This ELISA kit is a solid phase ELISA designed for quantitative determination. The STOP solution is 1M sulphuric acid. The wash buffer is 0.05 % Tween 20 in PBS, pH 7.4. The ELISA kit dose not contain (sodium) azide, thimerosal, 2-mercaptoethanol (2-ME). Part of the reagents contain BSA. PBS (pH 7.0-7.2) or 0.9% physiological saline will be used as dilution buffer. 10mL of wash solution concentrate (100×) with 990mL of deionized or distilled water will be dilute to prepare 1000mL of wash solution (1×). If crystals have formed in the concentrate, warm to room temperature and mix gently until the crystals have dissolved. The 1× wash solution is stable for 2 weeks at 2-8°C.

#### **Assessment of anthropometric measurements, dietary and physical activity**

Anthropometric measurements (weight, height, body mass index), dietary and physical activity data were measured at baseline and end of the study.

Dietary intake was evaluated by three-day dietary records. Dietary data were analyzed by Nutritionist IV software (First Databank, San Bruno, CA, USA). Physical activity was assessed by International Physical Activity Questionnaires (IPAQ) (15).

Participants were advised not to change their usual diet and physical activity during the study period.

#### **Statistical analyses**

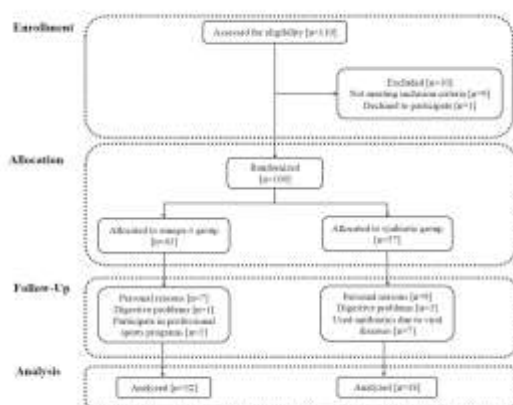
Normality of variables assessed by Kolmogorov–Smirnov test and Q-Q plot. The logarithmic transformation was used for the normalization of the positively skewed data. Quantitative variables were presented as mean ± standard deviation (SD) while qualitative variables were as frequency (percentage). To compare quantitative variables between the

groups, independent samples t-test and within-the-group comparisons, the paired sample t-test analysis were used. For determining any differences between the two groups, we used the analysis of covariance (ANCOVA) test which was adjusted by baseline values and confounding factors. For all tests, two-sided p-values less than 0.05 is considered statistically significant. All statistical analyses were carried out by using SPSS statistical software version 20 (IBM, Chicago, IL, USA).

## Results

Among 100 subjects, eleven subjects in the omega-3 group and 19 subjects in the synbiotic group dropped out. Twelve participants did not want to continue taking the drug for personal reasons, digestive problems occurred in six participants, five subjects used antibiotics due to viral diseases, and seven subjects participate in professional sports programs.

Finally, 32 subjects in omega-3 group (17 girls and 15 boys) and 38 subjects in synbiotic group (15 girls and 23 boys) completed the study and were included in the final analysis. (Figure 1).



**Figure 1.** Flow chart of the clinical trial.

Baseline information of participants are detailed in Table 1. Except weight, none of the other baseline variables showed significant differences between two groups.

**Table 1.** Characteristics of the participants.

Variables	Total(n=70)	Synbiotic (n=38)	Omega-3(n=32)	P-value
Gender( Girl / Boy)	32/38	15/23	17/15	0.26
Boy (n(%))	38 (54.29%)	23 (60.52%)	15 (46.88)	0.26
Age	12.87 ± 2.49	12.45 ± 2.32	13.38 ± 2.62	0.124
Height (cm)	156.76 ± 13.89	154.32 ± 13.64	159.68 ± 13.8	0.108
Weight (kg)	49.50 ± 15.99	45.94 ± 13.74	53.75 ± 17.60	0.041
BMI (kg/m <sup>2</sup> )	19.70 ± 4.04	18.88 ± 3.37	20.68 ± 4.57	0.062
MET (m/hr)	4038.77 ± 4804.85	4449.16 ± 5116.6	3551.44 ± 4437.14	0.44

Data presented as mean ± SD. BMI=Body Mass Index, MET=Metabolic Equivalent of Task

The within and between group analysis of macro and micronutrient intake are presented in Table 2. All nutrients were normal except EPH, vitamin A, Beta-carotene and vitamin D. The median value and the interquartile range were reported for continuous non-normal data. To perform the hypothesis test, due to the necessity of establishing normality, the log-transformed data were used. Nutrients intake during the study was compared between the two groups and no significant difference was observed.

**Table 2.** Comparison of baseline and endpoint nutrient intake in the treatment and control groups

Variables	Synbiotic (n=38)		P	Omega 3 (n=32)		p	p <sup>1</sup>	p <sup>2</sup>
	before	after		before	after			
Energy (kcal)	1630.90 ± 356.78	1434.76 ± 373.46	0.02	1494.36 ± 326.75	1400.28 ± 377.51	0.17	0.72	0.70
Protein (g)	80.00 ± 13.70	68.29 ± 27.78	0.08	74.34 ± 29.55	70.72 ± 36.26	0.66	0.38	0.75
Carbohydrate (g)	239.52 ± 64.66	207.86 ± 58.20	0.01	220.36 ± 57.55	197.56 ± 44.96	0.01	0.42	0.42
Total fat (g)	39.31 ± 16.70	37.17 ± 14.40	0.56	35.95 ± 14.68	37.21 ± 14.97	0.73	0.86	0.99
SFA (g)	13.37 ± 8.46	11.73 ± 5.87	0.31	11.76 ± 7.09	12.85 ± 7.72	0.57	0.74	0.58
MUFA (g)	11.47 ± 5.20	9.87 ± 4.86	0.17	10.50 ± 4.79	10.11 ± 5.54	0.88	0.86	0.85
PUFA (g)	9.65 ± 3.68	7.71 ± 2.13	0.01	9.00 ± 3.71	7.62 ± 1.98	0.06	0.82	0.84
EPHA (g)	0.0 [0.0,0.01]	0.0 [0.0,0.01]	0.66	0.0 [0.0,0.0]	0.0 [0.0,0.0]	0.01	0.74 <sup>a</sup>	0.53 <sup>a</sup>
DHA (g)	0.04 ± 0.17	0.03 ± 0.11	0.68	0.01 ± 0.02	0.04 ± 0.12	0.30	0.13	0.81
Vitamin A (µg)	264.23 [112.45,478.11]	265.86 [147.49,430.11]	0.00	364.93 [290.46,575.1]	326.43 [162.23,550.46]	0.00	0.17 <sup>a</sup>	0.20 <sup>a</sup>
Beta carotene (µg)	10.80 [1.77,163.72]	10.13 [1.77,76.37]	0.38	30.15 [1.45,382.58]	21.12 [2.45,82.80]	0.50	0.79 <sup>a</sup>	0.65 <sup>a</sup>
Vitamin E (mg)	2.77 ± 1.49	2.81 ± 2.81	0.93	3.25 ± 2.56	2.13 ± 1.50	0.04	0.13	0.23
Vitamin C (mg)	52.48 ± 42.49	57.91 ± 52.91	0.60	59.78 ± 47.21	57.26 ± 41.91	0.83	0.80	0.96
Vitamin D (µg)	0.0 [0.0,2.53]	0.31 [0.0,2.53]	0.99 <sup>b</sup>	0.07 [0.0,2.53]	0.0 [0.0,2.53]	0.89 <sup>b</sup>	0.72 <sup>a</sup>	0.42 <sup>a</sup>

Data presented as mean ± SD for continuous normal data or median [Q1, Q3] for continuous non-normal data. p<sup>1</sup>: Within-group P-value, g: Between baseline of two group comparisons, P<sup>2</sup>: Between endpoint of two group comparisons. a: Analyzed on Log-transformed data, b: Related samples Wilcoxon signed rank test, c: Independent samples Mann-Whitney U test.

Table 3 shows the within and between-group analysis of MAD levels in two groups. There were no significant differences between MAD levels in the omega-3 and synbiotic groups at baseline (P= 0.29). The levels of MDA decreased in two groups. However, the decrease in MAD levels in the synbiotic group was greater than the omega-3 group. There were no

significant differences between the mean changes in MAD levels between the two groups ( $P=0.75$ ). After adjustment the analysis with confounder in three models (model 1: adjusted with baseline, model 2: adjusted with baseline, sex, age, model 3: adjusted with baseline, sex, age, BMI, kcal and IPAQ score) significant reduction effects were observed with synbiotic consumption.

Table 3. The effect of synbiotic on TAC levels in comparison with omega-3 group.

Variables	Before	After	Change	P*	P <sup>1</sup> (Model 1)	P <sup>2</sup> (Model 2)	P <sup>3</sup> (Model 3)
TAC ( $\mu\text{mol/L}$ )							
Synbiotic (n=38)	839.78 $\pm$ 133.80	903.37 $\pm$ 111.90	63.59 $\pm$ 132.61	0.005		0.27	0.09
Omega 3 (n=32)	898.63 $\pm$ 86.45	953.28 $\pm$ 100.42	54.65 $\pm$ 97.87	0.004			0.07
P**	0.04	0.06	0.75				

TAC, total antioxidant capacity; \* Within-group comparison; \*\* Between two group comparisons; 1 model 1: adjusted for baseline; model 2: adjusted for baseline, sex, age; model 3: adjusted for baseline, sex, age, BMI, energy, vitamins with antioxidant properties and IPAQ score.

## Discussion:

The present study aimed to assess whether a synbiotic supplementation had beneficial effects on MDA as marker of oxidative stress in healthy adolescents who were exposed to air pollution. The findings of the current study showed that the levels of MDA significantly decreased at the end of the intervention in the synbiotic group. After adjustment the analysis with confounder in three models, significant reduction effects were observed with synbiotic consumption in comparison with omega 3 consumption.

Plasma and urinary MDA levels are mostly measured as a biomarker of systemic oxidative stress (16). MDA is generated mainly by arachadonic acid and docosahexaenoic acid that is one of the final products of lipid peroxidation. Air pollution and particular matter with an aerodynamic diameter of 2.5  $\mu\text{m}$  or smaller has been correlated with higher urinary MDA levels (4).

Several studies showed that the consumption of omega-3 fatty acid supplements could have beneficial effects on MDA levels in different population (17-19). The main purpose of the present study was to determine the effects of

synbiotics compared to omega-3, that beneficial effects of omega 3 have been shown in many studies to reduce MDA levels.

Study on patients with type II diabetes showed that consumption of the synbiotic bread for 8 weeks had beneficial effects on MDA levels (20).

Meta-analysis on 23 research papers showed that probiotics improved hepatic superoxide dismutase (SOD) and glutathione peroxidase (GSH-PX) activity and decreased hepatic MDA level (21). According to meta-analysis of randomized controlled trials on patients with psychiatric disorders, consumption of probiotic had beneficial impact on MDA levels (22). Meta-analysis on pregnant women with gestational diabetes (GDM) showed that probiotics supplementation might reduce the levels of MDA. However, some factors including inter-study heterogeneity and the small number of included studies decrease the reliability of the results (23). One systematic review and meta-analysis on eleven included studies assessed the effect of probiotic supplementation on some oxidative stress biomarkers on adult. Results revealed that probiotic may decrease the MDA levels. However, results should be interpreted with caution because of high heterogeneity. More studies are required to clarify the impact of probiotics on oxidative stress biomarkers (24). Evidence has shown that oxidative stress and endothelial damage increases the lipids oxidation that it leads to increased MDA levels. So, increasing the levels of MDA can be considered as indicator of lipid peroxidation. Previous studies showed that probiotics and synbiotics can improve lipid profiles and reduce the amount of oxidized LDL that is MDA enhancing agents. Probiotics and synbiotics can reduce total cholesterol, LDL and triglyceride and also increase HDL levels. Therefore, it can be concluded that probably the effects of synbiotics on MDA levels is due to the beneficial effects on lipid profiles (24, 25). Modulation of intestinal flora by the probiotic bacteria create a balance between inflammatory

and anti-inflammatory responses and moderates the production of oxidative biomarkers (26).

However some studies did not show any beneficial effects of synbiotics on MDA levels. Study on pregnant women with GDM showed that taking daily synbiotic capsule for 6 weeks had no significant beneficial effect on MDA levels (27). A randomized double-blind placebo-controlled clinical trial on patients with rheumatoid arthritis did not show any significant effect of daily consumption of probiotic for 8 weeks on MDA levels (10).

The differences between results may be due to differences in the type and dosage of probiotic and prebiotic in capsule, duration of the intervention, the study participants, health condition, sample size, and baseline characteristics (24, 28). Studies showed that multistrain probiotic is more effective than single strain and greater dosage of probiotics has greater therapeutic effect (29).

Air pollution is a major global health problem, and children are particularly vulnerable to its adverse effects. The use of dietary supplements may provide an effective strategy for reducing the harmful effects of air pollution. However, it is important to note that dietary supplements cannot be considered as a substitute for a healthy diet and lifestyle. Further studies are needed to investigate the long-term effects of synbiotic supplements on oxidative stress and adverse effects of air pollution on health.

One of the most important strengths of the present study is that it is the first study that investigated the effect of synbiotic supplementation on MDA levels in healthy children and adolescents who were exposed to air pollution. The limitations of the present study are diet underreporting and the lack of long-term follow up and not examining the pubertal status of participants.

### Conclusion

The levels of MDA significantly reduced with synbiotic consumption in comparison with omega-3 after adjustment the analysis with confounder. We suggest further clinical trial on larger sample size for evaluating the effects of

synbiotic on toxic air pollutants and biomarker of oxidative stress in children and adolescents.

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