

Article

Dietary and Antioxidant Vitamins Limit the DNA Damage Mediated by Oxidative Stress in the Mother–Newborn Binomial

Hector Diaz-Garcia ^{1,2}, Jenny Vilchis-Gil ^{3,4} , Pilar Garcia-Roca ⁵, Miguel Klünder-Klünder ⁶ ,
Jacqueline Gomez-Lopez ⁷, Javier T. Granados-Riveron ¹ and Rocio Sanchez-Urbina ^{1,8,*} 

- ¹ Unidad de Investigación en Malformaciones Congénitas, Hospital Infantil de Mexico Federico Gómez, Mexico City 06720, Mexico; hecdiazgar@gmail.com (H.D.-G.); javiertgranados@gmail.com (J.T.G.-R.)
- ² Sección de Estudios de Posgrado e Investigación de la Escuela Superior de Medicina del Instituto Politécnico Nacional, Mexico City 11340, Mexico
- ³ Unidad de Investigación Epidemiológica en Endocrinología y Nutrición, Hospital Infantil de Mexico Federico Gómez, Mexico City 06720, Mexico; jvilchis@himfg.edu.mx
- ⁴ Facultad de Medicina, Universidad Nacional Autónoma de Mexico, Mexico City 04510, Mexico
- ⁵ Unidad de Investigación y Diagnóstico en Nefrología y Metabolismo Mineral Ósea, Hospital Infantil de Mexico Federico Gómez, Mexico City 06720, Mexico; mipgr5910@gmail.com
- ⁶ Subdirección de la Gestión de la Investigación, Hospital Infantil de Mexico Federico Gómez, Mexico City 06720, Mexico; klunderk@gmail.com
- ⁷ Hospital Militar de Especialidades de la Mujer y Neonatología, Secretaria de la Defensa Nacional, Mexico City 11200, Mexico; drajackiegomezlopez@yahoo.com.mx
- ⁸ Escuela Superior de Medicina del Instituto Politécnico Nacional, Mexico City 11340, Mexico
- * Correspondence: roci0404@gmail.com; Tel.: +52-55-5228-9917 (ext. 4302)



Citation: Diaz-Garcia, H.; Vilchis-Gil, J.; Garcia-Roca, P.; Klünder-Klünder, M.; Gomez-Lopez, J.; Granados-Riveron, J.T.; Sanchez-Urbina, R. Dietary and Antioxidant Vitamins Limit the DNA Damage Mediated by Oxidative Stress in the Mother–Newborn Binomial. *Life* **2022**, *12*, 1012. <https://doi.org/10.3390/life12071012>

Academic Editors: Tibor Ertl and Dénes Molnár

Received: 17 June 2022

Accepted: 3 July 2022

Published: 8 July 2022

Publisher's Note: MDPI stays neutral with regard to jurisdictional claims in published maps and institutional affiliations.



Copyright: © 2022 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (<https://creativecommons.org/licenses/by/4.0/>).

Abstract: During pregnancy, appropriate nutritional support is necessary for the development of the foetus. Maternal nutrition might protect the foetus from toxic agents such as free radicals due to its antioxidant content. In this study, 90 mothers and their children were recruited. DNA damage mediated by oxidative stress (OS) was determined by the levels of 8-hidroxy-2'-deoxyguanosine (8-OHdG) in the plasma of women and umbilical cord blood. The mothers and newborns were categorised into tertiles according to their 8-OHdG levels for further comparison. No relevant clinical differences were observed in each group. A strong correlation was observed in the mother–newborn binomial for 8-OHdG levels ($Rho = 0.694$, $p < 0.001$). In the binomial, a lower level of 8-OHdG was associated with higher consumption of calories, carbohydrates, lipids, and vitamin A ($p < 0.05$). In addition, the levels of 8-OHdG were only significantly lower in newborns from mothers with a higher consumption of vitamin A and E ($p < 0.01$). These findings were confirmed by a significant negative correlation between the 8-OHdG levels of newborns and the maternal consumption of vitamins A and E, but not C ($Rho = -0.445$ ($p < 0.001$), -0.281 ($p = 0.007$), and -0.120 ($p = 0.257$), respectively). Multiple regression analysis showed that the 8-OHdG levels in mothers and newborns inversely correlated with vitamin A ($\beta = -1.26$ ($p = 0.016$) and -2.17 ($p < 0.001$), respectively) and pregestational body mass index ($\beta = -1.04$ ($p = 0.007$) and -0.977 ($p = 0.008$), respectively). In conclusion, maternal consumption of vitamins A and E, but not C, might protect newborns from DNA damage mediated by OS.

Keywords: pregnancy; vitamin A; 8-hydroxy-2'-deoxyguanosine; DNA damage; oxidative stress

1. Introduction

Quality and quantity of diet depend on the interplay between complex factors, such as the environment, personal economics, cultural background, and food availability [1]. During pregnancy, nutritional changes take place to supply the demands of both the mother and the foetus, and they are important for the normal development of the foetus [2]. Besides the mother's diet, the foetus is susceptible to damage by maternal diseases, such as

type 2 diabetes (T2D), obesity [3–5], or smoking [6,7], and the consumption of alcohol [8,9]. Under these conditions, free radicals (FR) are overproduced and accumulate in cells.

FR are molecules with an unpaired electron in their orbitals, which they donate to biomolecules, such as proteins, lipids, or DNA, to stabilise their own structure [10] while altering the structure and function of the biomolecule. Oxidative stress (OS) is a physiological status characterised by an accumulation of FR due to an imbalance in their production and elimination [11]. OS represents a danger to the organs and tissues of the mother and the foetus, but the antioxidant enzymatic system (superoxide dismutase, glutathione peroxidase, catalase, etc.) and the non-enzymatic system (transferrin, lactoferrin, phytochemicals, vitamins, etc.) limit FR overproduction [12–15].

OS might cause foetus damage [16] or predispose the progeny to develop certain diseases during their lifetime, such as cardiovascular diseases, T2D, or cancer [17]. Maternal diet might be a factor that influences the predisposition of the progeny toward these diseases.

Among the nitrogenous bases of DNA, guanine is the most susceptible to oxidation by OS [18]. Guanine oxidation produces 8-hydroxy-2'-deoxyguanosine (8-OHdG), which is used as a marker for OS-mediated DNA damage [19]. Increased 8-OHdG is associated with the progression or prognosis of cardiovascular diseases, T2D [20,21], cancer [22,23], and other diseases in adults [24–29]. In pregnant women, high levels of 8-OHdG have been associated with restriction of foetal growth [30,31], neural tube defects [32], and orofacial clefts [33] in the progeny. On the other hand, in mothers, high 8-OHdG levels were associated with gestational diabetes mellitus (GDM) [34,35], and more recently, it was observed in pregnant women infected by severe acute respiratory syndrome coronavirus 2 [36].

Food antioxidants such as vitamins A, C, and E have been widely studied for their ability to regulate and maintain physiological levels of OS in the body [37]. These vitamins, when used in highly pro-oxidative conditions (smokers), decreased the levels of 8-OHdG [38]. However, there is limited information about the effect of the maternal diet on OS-mediated DNA damage in mother–newborn binomials. The aim of this study was to determine whether the consumption of calories, macronutrients, and the vitamins A, C, and E during pregnancy modified OS-mediated DNA damage at the end of pregnancy in both the mother and the child. In this study, there was a strong correlation between 8-OHdG levels in the mother–child binomial, and the intake of vitamin A during pregnancy decreased 8-OHdG levels in the mothers and their children.

2. Materials and Methods

2.1. Participants

This study was performed with 90 healthy women and their children. Participants were recruited between January 2016 and December 2017. All women signed an informed consent form. The study was conducted in accordance with the latest version of the Declaration of Helsinki, and the protocol was approved by the Ethics and Biosecurity committees of the Hospital Infantil de Mexico Federico Gómez. We included women who did not have any nutritional conditions before pregnancy, delivered 38 to 40 weeks from their last menstruation, and had adequate prenatal control, including monthly medical consultations from the first trimester of pregnancy and a minimum of two normal ultrasonography results. Women who had pre-eclampsia, type 1 diabetes, T2D, or GDM were excluded. Data on the weight of the women before pregnancy were obtained from their medical history record. A physician measured the heights of the women by using a stadiometer (SECA, Hamburg, Germany) at the time of recruitment. The anthropometric data on weight and length, gestational age, mode of delivery, and sex of newborns were registered at birth. Mothers were categorised according to their pregestational body mass index (BMI, kg/m²) into normal-weight, BMI 18.5–24.9; overweight, BMI 25–29.9; and obese, BMI 30 and above. The pregestational record of smoking (number of cigarettes per day and period during the pregnancy) and alcohol consumption were collected from responses to direct questions during the medical examination.

2.2. Frequency of Food Consumed

A food frequency questionnaire to assess regular food intake was administered by a trained doctor to all participants in the third trimester before labour, as previously described [39]. The questionnaire was validated for estimated folate intake in the Mexican population. Briefly, the amount of food consumed was calculated in terms of the unit of measurement used (i.e., piece, cup, plate, or spoon) and the size of the unit (i.e., small, medium, or large). The frequency of consumption was calculated in grams or millilitres per day. The participants' daily intake of energy (calories per day), macronutrients (carbohydrates, lipids, and proteins), and vitamins (A, C, and E) were calculated using the Food Processor SQL programme (version 10.9.0, 2011; ESHA Research, Salem, Oregon) and Mexican food tables, including data on traditional Mexican food [40]. For the statistical analysis, missing data on vitamins ($n = 2$) and calorie values above 2.5 standard deviation (SD) ($n = 3$) were excluded.

2.3. Blood Samples

During the last medical examination before delivery, 5 mL peripheral blood was collected from the women. Immediately after birth, the umbilical cord was clamped, and 5 mL blood samples were collected from it. All blood samples were collected in ethylenediaminetetraacetic acid-containing tubes, centrifuged at $1800 \times g/15$ min, and subjected to protein precipitation with 20% trichloroacetic acid (50:50 *v/v*). Then, centrifugation was repeated at $3600 \times g/5$ min at 4 °C. The plasma was stored at -80 °C until 8-OHdG determination.

2.4. 8-OHdG Quantification

The 8-OHdG level was determined in the plasma by immunofluorescence using the 8-hydroxy-2'-deoxyguanosine enzyme immunoassay (EIA) kit (CEDERLANE, Burlington, NC, USA) as previously reported [41]. Standard curves were constructed starting with a bulk standard of 8-OHdG (30 ng/mL, 8-hydroxy-2-deoxy Guanosine EIA Standard, Cat# CL89120KC) and 8 dilutions (3000 pg/mL to 10.3 pg/mL), and the assays were carried out according to the manufacturer's instructions. Briefly, 50 μ L of plasma, the EIA buffer, the 8-OHdG standard, and the 8-OHdG-acetylcholinesterase tracer were added to the wells. The monoclonal antibody against 8-OHdG was added, and the plate was incubated for 18 h at 4 °C followed by several washes with wash buffer. Then, 200 μ L of Ellman's reagent was added to each well. Optical densities were determined at 405 nm.

2.5. Clinical and Nutrient Profiles Based on 8-OHdG Tertiles

For the analysis, tertiles were constructed from the 8-OHdG values of the mothers and the newborns. For the mothers, tertile 1 was 1.55–3.09 ng/mL, tertile 2 was 3.13–4.23 ng/mL, and tertile 3 was 4.29–9.78 ng/mL, and for newborns, tertile 1 was 1.55–3.38 ng/mL, tertile 2 was 3.41–4.54 ng/mL, and tertile 3 was 4.59–12.83 ng/mL. Each tertile comprised 30 mothers and newborns (Figure 1). For micronutrients and macronutrients, the percentages of adequate intake were estimated using the recommended Dietary Reference Intakes from the Standing Committee On The Scientific Evaluation Of Dietary Reference Intakes (National Academy of Science, Washington, DC, USA) [42].

2.6. Statistical Analyses

Descriptive statistics, including mean, SD, median, interquartile range, and frequency, were used to describe the baseline characteristics of mothers and newborns. Medians and tertile ranges were used to report the daily calories obtained from the food consumed; amounts of proteins, carbohydrates, and fats; and the estimated consumption of vitamins A, C, and E. Based on a pre-exploratory variable analysis to identify their distributions, we used the Kruskal–Wallis rank sum test following a multiple comparison of p-values adjusted with the post-hoc Bonferroni method. Fisher's exact test and the χ^2 test were used to compare categorical variable differences. Quantile regression models were used

to evaluate the association of clinical characteristics, macronutrients, and micronutrients with 8-OHdG levels. Data analysis and visualisation was performed in R version 3.6.2 (12 December 2019, Bell Laboratories, Murray Hill, NJ, USA) and STATA/SE 17.0 statistical programme (STATA Corp., College Station, TX, USA). p -values < 0.05 were considered to indicate statistically significant differences.

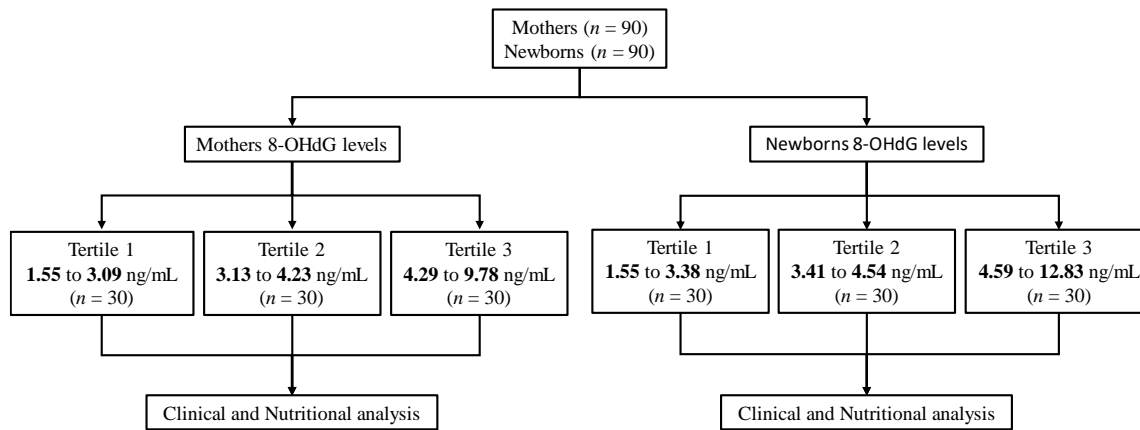


Figure 1. Group distribution by tertile of the 8-OHdG levels of mothers and newborns for nutritional analysis. 8-OHdG, 8-hydroxy-2'-deoxy-guanosine.

3. Results

3.1. Subject Characteristics

This study was performed with 90 women and their newborns. The mean age of the mothers was 24.1 ± 5.2 years, their mean pregestational weight was 63.8 ± 11.1 kg, and their mean pregestational BMI was 26.1 ± 4.0 . Of them, 43.3% were normal-weight, 33.3% were overweight, and 23.3% were obese. Smoking during the first trimester of pregnancy was reported by 10% of the mothers, whereas only 1.1% ($n = 1$) reported alcohol consumption. Multivitamin supplements were consumed during pregnancy by 91.1% of women. The mean age of the newborns was 38.7 ± 1.3 weeks, their mean weight was 3188 ± 435 g, and their mean height was 49.4 ± 2.3 cm.

The characteristics of mothers and newborns for each 8-OHdG tertile are shown in Table 1. A significant proportion of normal-weight mothers were observed in tertile 1 compared with tertile 2 ($p = 0.035$). No other significant differences in clinical characteristics among mothers were observed.

Among the newborns classified by the tertiles for the mothers' 8-OHdG levels, males were more frequent in tertile 1 than in tertile 2, and caesarean deliveries were more frequent in tertile 3 than in tertile 2. No other significant differences were observed in these groups (Table 1). On the other hand, among newborns classified according to the tertiles of their own 8-OHdG levels, newborns were significantly older in tertile 3 than in tertile 2, and caesarean deliveries were more frequent in tertile 1 than in tertile 2 (Table 1). No other significant differences were detected in the clinical characteristics of newborns in these groups.

Table 1. Clinical features of mothers and newborns for each 8-OHdG tertile.

Mothers	Mothers 8-OHdG			p-Value			Newborns 8-OHdG			p-Value		
	Tertile 1 Mean ± SD	Tertile 2 Mean ± SD	Tertile 3 Mean ± SD	a	b	c	Tertile 1 Mean ± SD	Tertile 2 Mean ± SD	Tertile 3 Mean ± SD	a	b	c
Age (years) [§]	23.1 ± 6.2	24.7 ± 4.9	24.6 ± 4.5	0.250	0.301	1	23.0 ± 5.6	25.4 ± 5.8	24.0 ± 4.0	0.164	0.919	1
Pregestational weight (kg) [§]	61.0 ± 12.1	66.1 ± 10.5	64.4 ± 10.3	0.167	0.595	1	61.5 ± 11.2	67.3 ± 10.8	62.8 ± 10.7	0.085	1	0.392
Pregestational BMI (kg/m ²) [§]	24.9 ± 4.4	27.2 ± 3.9	26.1 ± 3.5	0.156	0.950	1	25.8 ± 4.4	27.1 ± 4.2	25.4 ± 3.4	0.929	1	0.432
Normal-weight (n, %) ^{§§}	17 (56.7)	8 (26.7)	14 (46.7)	0.035	0.605	0.179	16 (53.3)	10 (33.3)	13 (43.3)	0.192	0.605	0.595
Overweight (n, %) ^{§§}	7 (23.3)	13 (43.3)	10 (33.3)	0.170	0.567	0.595	6 (20.0)	11 (36.7)	13 (43.3)	0.251	0.094	0.792
Obese (n, %) ^{§§}	6 (20.0)	9 (30.0)	6 (20.0)	0.552	1	0.552	8 (26.7)	9 (30.0)	4 (13.3)	1	0.333	0.209
Smoking (n, %) ^{§§§}	6 (20.0)	3 (10.0)	0	-	-	-	8 (26.7)	1 (3.3)	0	-	-	-
Multivitamin suppl. (n, %) ^{§§§}	26 (86.7)	28 (93.3)	28 (93.3)	0.667	0.667	1	27 (90.0)	28 (93.3)	27 (90.0)	1	1	1
Newborns												
Gestational age (weeks) [§]	38.8 ± 1.4	38.5 ± 1.3	38.8 ± 1.1	0.808	1	1	38.8 ± 1.3	38.2 ± 1.4	39.1 ± 0.9	0.450	0.709	0.026
Weight (g) [§]	3286 ± 424	3189 ± 479	3088 ± 389	1	0.468	1	3226 ± 448	3157 ± 415	3180 ± 452	1	1	1
Height (cm) [§]	49.8 ± 2.4	49.3 ± 2.8	49.3 ± 1.7	1	1	1	49.3 ± 2.9	49.4 ± 2.2	49.6 ± 1.6	1	1	1
Sex (male, n, %) ^{§§}	18 (60.0)	9 (30)	16 (53.3)	0.036	0.794	0.115	14 (46.7)	14 (46.7)	15 (50.0)	1	1	1
Caesarean delivery (n, %) ^{§§}	6 (20.0)	5 (16.7)	13 (43.3)	1	0.094	0.047	11 (36.7)	3 (10.0)	10 (33.3)	0.030	1	0.057

[§] Kruskal–Wallis rank sum test with Dunn Kruskal–Wallis multiple comparison of p-values adjusted with the Bonferroni method. ^{§§} Fisher’s exact Test. ^{§§§} Pearson’s Chi-squared test with Yates’ continuity correction. Tertile comparisons: tertile 1 vs. tertile 2 (a), tertile 1 vs. tertile 3 (b), tertile 2 vs. tertile 3 (c). BMI, body mass index; SD, standard deviation.

3.2. Correlation of 8-OHdG Levels between Mothers and Newborns

We observed a strong correlation between the 8-OHdG levels of mothers and newborns ($p < 0.001$) (Figure 2). No significant correlations were detected between the 8-OHdG levels of mothers or newborns and the mothers' age, pregestational weight, pregestational BMI, or the newborns' age, weight, and height.

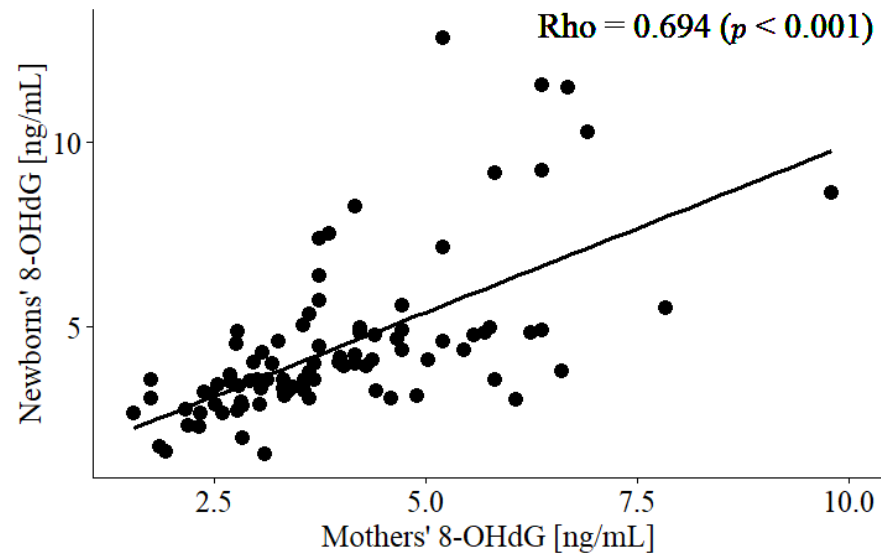


Figure 2. Correlation between the 8-OHdG concentrations of mothers and newborns.

3.3. Nutritional Differences among Mother Tertiles in the Mothers 8-OHdG Group

Mothers in tertile 3 of the mothers 8-OHdG group consumed significantly lower amounts of calories, carbohydrates, lipids, proteins, and vitamin A, but not vitamin C and E, compared with mothers in tertile 1 (Table 2). No other significant differences were observed in macronutrient and micronutrient consumption by mothers belonging to these tertiles.

Table 2. Nutrient differences between mother tertiles in the mothers 8-OHdG group.

	Mothers 8-OHdG Tertiles			<i>p</i> -Value [§]		
	Tertile 1 Median (p25, p75)	Tertile 2 Median (p25, p75)	Tertile 3 Median (p25, p75)	a	b	c
	Calories (kcal/d)	2396 (1712, 3283)	1754 (1551, 2345)	1645 (1429, 1867)	0.202	0.002
Carbohydrates (g/d)	332.4 (252.2, 478.7)	286.4 (249.7, 366.4)	266.3 (216.9, 297.0)	0.633	0.021	0.447
% kcal/d	56.9 (53.3, 59.7)	60.3 (55.9, 63.6)	61.0 (54.5, 63.9)	0.053	0.086	1
Lipids (g/d) %	69.9 (53.9, 102.6)	48.6 (43.4, 69.5)	45.1 (39.0, 46.9)	0.080	<0.001	0.238
kcal/d	26.1 (24.4, 27.8)	24.1 (22.3, 27.4)	23.5 (21.6, 26.9)	0.233	0.035	1
Proteins (g/d) %	102.7 (70.9, 150.6)	64.2 (57.6, 94.1)	60.5 (55.8, 83.7)	0.053	0.002	0.990
kcal/d	17.0 (15.0, 18.1)	15.9 (13.8, 16.9)	15.7 (13.7, 18.6)	0.076	0.933	0.666
Vitamin A (ER/d) %	859.1 (545.7, 1224.8)	521.6 (428.4, 735.5)	489.3 (364.9, 603.7)	0.102	0.006	1
adequacy	171.8 (109.1, 244.9)	104.3 (85.7, 147.1)	97.9 (72.9, 120.7)	0.102	0.006	1
Vitamin C (mg/d) %	138.2 (113.4, 222.7)	198.3 (147.9, 226.2)	157.0 (137.2, 172.8)	0.111	1	0.195
adequacy	230.2 (189.1, 371.2)	330.6 (246.6, 377.0)	261.6 (228.5, 288.0)	0.111	1	0.195
Vitamin E (mg/d) %	4.26 (3.31, 5.13)	4.20 (3.51, 4.96)	3.69 (3.03, 4.39)	1	0.296	0.362
adequacy	35.4 (27.6, 42.7)	35.0 (29.3, 41.3)	30.8 (25.3, 36.6)	1	0.296	0.362

[§] Kruskal–Wallis rank sum test with Dunn Kruskal–Wallis multiple comparison of *p*-values adjusted with the Bonferroni method. Tertile comparisons: tertile 1 vs. tertile 2 (a), tertile 1 vs. tertile 3 (b), tertile 2 vs. tertile 3 (c). *p*, percentile.

3.4. Nutritional Differences among the Mother Tertiles in the Newborns 8-OHdG Group

Mothers in tertile 3 of the newborns 8-OHdG group consumed significantly lower amounts of calories, carbohydrates, lipids, proteins, vitamins A and E, but not vitamin C, compared with mothers in tertile 1 (Table 3). Additionally, the mothers in tertile 2 consumed similar amounts of protein to those in tertile 3 ($p > 0.05$) but lower than those in tertile 1 ($p < 0.05$). Lastly, mothers in tertile 2 consumed more vitamin A than those in tertile 3 ($p < 0.05$), but similar to those in tertile 1 ($p > 0.05$). No other significant differences in macronutrient and micronutrient consumption were observed between the mothers in this group (Table 3).

Table 3. Nutrient differences by mother tertiles in the newborns 8-OHdG group.

	Newborns 8-OHdG Tertile			<i>p</i> -Value [§]		
	Tertile 1 Median (p25, p75)	Tertile 2 Median (p25, p75)	Tertile 3 Median (p25, p75)	a	b	c
	Calories (kcal/d)	2446 (1787, 3283)	1772 (1539, 2344)	1616 (1334, 1816)	0.068	<0.001
Carbohydrates (g/d)	372.4 (269.0, 478.7)	281.9 (245.2, 352.7)	256.3 (201.1, 296.2)	0.076	<0.001	0.406
% kcal/d	57.4 (54.4, 60.2)	59.9 (56.9, 63.6)	60.6 (54.4, 62.6)	0.406	0.650	1
Lipids (g/d) %	73.3 (52.3, 102.8)	51.43 (42.24, 69.35)	44.85 (41.10, 47.22)	0.0912	<0.001	0.273
kcal/d	25.4 (23.3, 27.3)	23.79 (22.28, 27.50)	24.28 (22.96, 28.86)	0.754	1	1
Proteins (g/d) %	124.2 (77.2, 157.9)	68.3 (58.4, 98.9)	61.0 (56.3, 72.7)	0.034	<0.001	0.455
kcal/d	17.1 (14.9, 18.1)	15.9 (13.8, 17.7)	15.1 (13.8, 17.4)	0.334	0.243	1
Vitamin A (ER/d) %	853.3 (545.1, 1191)	590.4 (479.0, 964.4)	428.5 (364.9, 539.0)	0.499	<0.001	0.015
adequacy	170.6 (109.0, 238.2)	118.0 (95.8, 192.8)	85.7 (72.9, 107.8)	0.499	<0.001	0.015
Vitamin C (mg/d) %	202.3 (124.6, 248.7)	161.8 (132.0, 226.2)	154.0 (129.6, 172.2)	1	0.167	0.576
adequacy	337.2 (207.7, 414.5)	269.8 (220.0, 377.0)	256.7 (216.0, 287.0)	1	0.167	0.576
Vitamin E (mg/d) %	4.71 (3.65, 5.43)	3.87 (3.33, 4.77)	3.56 (2.90, 4.32)	0.179	0.005	0.655
adequacy	39.3 (30.4, 45.2)	32.3 (27.7, 39.8)	29.6 (24.2, 35.9)	0.179	0.005	0.655

[§] Kruskal–Wallis rank sum test with Dunn Kruskal–Wallis multiple comparison of *p*-values adjusted with the Bonferroni method. Tertile comparisons: tertile 1 vs. tertile 2 (a), tertile 1 vs. tertile 3 (b), tertile 2 vs. tertile 3 (c).

3.5. Correlation of Mother Vitamins and Newborns 8-OHdG Levels

We observed significant correlations between vitamin A and vitamin E consumption by the mothers and 8-OHdG levels in the newborns ($p < 0.001$ and $p = 0.007$, respectively) (Figure 3a,b). A negative but no significant correlation between vitamin C for the mothers and the 8-OHdG levels of newborns was observed ($Rho = -0.120$, $p = 0.257$).

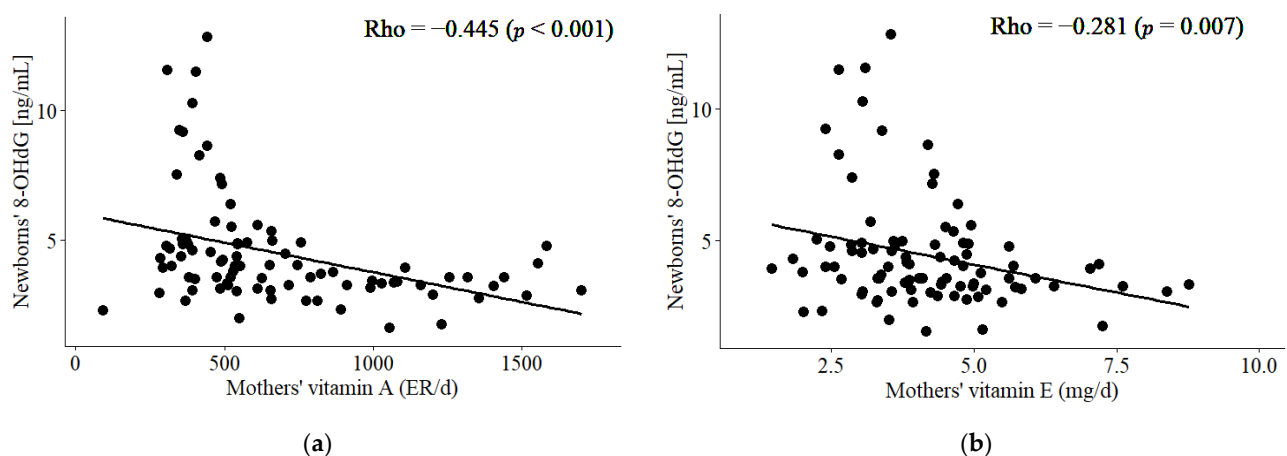


Figure 3. Correlation between vitamin A (a) and vitamin E (b) consumption by the mothers and 8-OHdG levels in the newborns.

3.6. 8-OHdG Variation by BMI and Vitamin A Consumption

The levels of 8-OHdG in mothers and newborns decreased by a unit in mothers with pregestational obesity. Additionally, the 8-OHdG level in mothers decreased by one unit in tertile 3 of vitamin A consumption, while that in newborns decreased by one and two units in tertiles 2 and 3 of vitamin A consumption, respectively (Table 4). All variations of 8-OHdG were independent of caloric and vitamin intake.

Table 4. Multiple regression analysis for the 8-OHdG levels in mothers and newborns.

Parameter	Mothers 8-OHdG (ng/mL) β (95% CI) ^a	<i>p</i> -Value	Newborns 8-OHdG (ng/mL) β (95% CI) ^a	<i>p</i> -Value
Pregestational BMI				
Normal-weight	Reference		Reference	
Overweight	−0.002 (−0.64 to 0.63)	0.995	0.048 (−0.56 to 0.66)	0.874
Obesity	−1.04 (−1.78 to −0.29)	0.007	−0.977 (−1.69 to −0.26)	0.008
Vitamin A (ER/d)				
Tertile 1 (91 to 475)	Reference		Reference	
Tertile 2 (485 to 745)	−0.123 (−0.90 to 0.66)	0.753	−1.15 (−1.90 to −0.41)	0.003
Tertile 3 (757 to 4028)	−1.26 (−2.28 to −0.24)	0.016	−2.17 (−3.15 to −1.19)	<0.001

^a Quantile regression model adjusted by caloric intake. CI, confidence interval.

4. Discussion

Pregnancy is characterised by increased OS [43], which is associated with metabolic activity and the development of the placenta [44]. DNA is especially susceptible to OS-mediated damage because guanines readily form adducts with FR giving rise to 8-OHdG [18]. During pregnancy, diet might increase or decrease OS, depending on its quality and quantity [17]; for example, the antioxidant properties of vitamins can keep OS in check [45].

In this work, the levels of 8-OHdG found in pregnant women and their newborns were similar to those reported previously [33,46–48]. Overweight and obesity in pregnant women have been associated with OS increment [49], OS-mediated DNA damage [50], and increased 8-OHdG levels [51]. However, when we compared the pregestational weight and BMI of mothers with their 8-OHdG levels (classified into tertiles), we did not observe significant associations (Table 1).

We observed that the 8-OHdG levels in mothers and newborns correlated strongly (Figure 2), which is in accordance with our previous study of another OS marker [39]. The source of 8-OHdG in pregnant women and newborns has not been identified yet [52], but Fukushima et al. showed that placental tissue stained positive for 8-OHdG [53]. Since the placenta has imperative functions, such as nutritional support and waste elimination [54], it might be an important, if not the major, source of 8-OHdG [30,52,55].

Maternal diet is an important regulator of OS since carbohydrate, lipid, and amino acid metabolism produces the superoxide radical (O_2^-), which through Haber–Weiss and Fenton’s reaction, produces hydrogen peroxide (H_2O_2) and the hydroxyl radical ($\bullet OH$), respectively [56]. Consequently, over-nutrition increases OS production [57] and $\bullet OH$ and H_2O_2 induce 8-OHdG formation [58,59]. In our study, we expected a significant increment in 8-OHdG when food consumption was higher; however, we observed lower levels of 8-OHdG when the consumption of calories, carbohydrates, lipids, and proteins was higher (Tables 2 and 3). This effect can only be explained by the antioxidant effects of the diet [60,61]. A study reported that daily fruit intake decreased urinary 8-OHdG secretion in adults [62], hinting that the antioxidant effects of vitamins might limit OS-mediated DNA damage [63]. Multiple studies have reported negative associations between different vitamins and 8-OHdG levels, e.g., plasma vitamin E levels and placental 8-OHdG [64], levels of vitamins E and C and 8-OHdG in the saliva of oral pre-cancer and cancer pa-

tients [65], serum vitamin C levels and urinary 8-OHdG [66], and plasma vitamin C levels and lymphocyte 8-OHdG levels in chronic renal disease [67].

To elucidate the effect of vitamins and maternal conditions on 8-OHdG levels, we developed beta analysis regressions. We found that obesity and the intake of vitamin A decreased 8-OHdG levels in mothers and newborns. This effect was maintained even after the analysis was adjusted for caloric intake, and it was more significant in the newborns (Table 4). This finding is contrary to a previous *in vitro* analysis, where vitamin A increased OS-mediated DNA damage with an increase in 8-oxo-7,8-dihydro-2'-deoxyguanosine (8-oxodG) [68], another oxidated derivative of guanine. Nonetheless, vitamin A regulates approximately 532 genes, of which some are involved in antioxidant pathways (Cooper/Zink superoxide dismutase, manganese superoxide dismutase, and glutathione peroxidase 2) [69]. Although vitamin A increased OS-mediated DNA damage *in vitro*, antioxidant genes might be activated during *in vivo* OS regulation. The negative association of BMI with 8-OHdG levels might be explained by an increase in the bioavailability of vitamin A in obese people [70,71].

Ascorbic acid and vitamin E have been employed for the treatment of high oxidative conditions such as those found in cardiovascular disease [72], cancer [73], chronic kidney disease [74,75], obesity [76,77], T2D [78], and in smokers [79]. Nonetheless, the effects of vitamin C and E are still controversial since they might play pro-oxidant [80–83], antioxidant [80,84–86], or no [87,88] roles. Specifically, reports on the roles of vitamins E and C in preventing guanine oxidation are mixed [66,81,89]. In this study, vitamins E and C, alone or in combination, failed to reduce 8-OHdG levels. Antioxidant effects of these vitamins have been observed mainly in vitamin-deficient people but not in non-deficient people [66,90]. Interestingly, higher levels of 8-OHdG were observed when the intake of vitamins A and E, but not vitamin C, was lower, and vice versa (Tables 2 and 3).

Alcohol consumption and smoking are common social practices, especially among young people [91]. In this study, we observed that 10% of women smoked until the first trimester of pregnancy, similar to reports for a Mexican-American population [40]. In some countries, as many as 25% of pregnant women smoke [92]. The proportion of smoking pregnant women in this study was similar to what was reported in a Spanish population [93]. Smoking is a prominent source of FR [94,95], which have deleterious effects on DNA [96,97], giving rise to 8-OHdG [98]. Smoking is associated with cardiovascular disease and cancer [99], and smoking during pregnancy has immediate or midterm effects on the foetus, including preterm pregnancy [100–102], low birth weight [102], congenital anomalies [103,104], chronic asthma [92,105–107], bronchiolitis [92,108], and psychiatric abnormalities [109–112]. Unfortunately, we could not follow the newborns of smoking mothers to confirm if they suffered from any of these conditions.

Predisposition to disease during adulthood has been associated with factors pertaining to the mother during the prenatal stage (foetal programming). Accordingly, we hypothesised that a diet rich in vitamins might modify the 8-OHdG levels during pregnancy in the mother–newborn binomial. Previous studies have proposed 8-OHdG as an OS maker in rheumatoid arthritis [48] and atherosclerotic plaque development [27], and as a risk factor for cardiovascular disease [29], metabolic syndrome [28], small-cell lung carcinoma [23], progression of hepatocellular carcinoma [22], and poor glycaemic control of T2D [21]. Consequently, higher levels of 8-OHdG in the progeny due to lower intake of vitamin-rich food by the mother might predispose the child to develop certain diseases in adulthood.

This study had some limitations. Since vitamin consumption was determined by a food frequency questionnaire, it was difficult to establish a precise and objective association between vitamins and 8-OHdG levels since factors like lower absorption rate [113], altered vitamin metabolism [114–116], or increased elimination rate [114,117] might modify the bioavailability of vitamins.

5. Conclusions

We found a strong correlation between 8-OHdG levels in mothers and newborns. The intake of vitamins A and E, but not C, by the mother might have a greater protective effects against OS-mediated DNA damage in newborns than in mothers.

Author Contributions: Conceptualisation, R.S.-U.; methodology, P.G.-R.; formal analysis, J.V.-G. and H.D.-G.; investigation, H.D.-G.; writing—original draft preparation, H.D.-G.; writing—review and editing, R.S.-U. and J.T.G.-R.; visualisation, M.K.-K.; supervision, J.G.-L.; funding acquisition, R.S.-U. All authors have read and agreed to the published version of the manuscript.

Funding: This study was funded by an internal grant (Government Grant) from the Hospital Infantil de Mexico Federico Gómez, Mexico (Register Number: HIM/2016/031).

Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki and approved by the Institutional Ethics Committee of the Hospital Infantil de Mexico Federico Gómez (Register Number: HIM/2016/031/25 January 2016).

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: The set of raw data analysed is available for other research studies upon application.

Acknowledgments: The author Hector Diaz-Garcia acknowledges the support of the Programa Nacional de Posgrados de Calidad of CONACyT Mexico (grant number: 420044) and the Beca de Estímulo Institucional de Formación de Investigadores program from the Instituto Politécnico Nacional (Mexico). The authors thank to the Department of Research of the Hospital Infantil de Mexico for their support for the development of this study.

Conflicts of Interest: The authors declare no conflict of interest.

References

- Alkerwi, A.A.; Vernier, C.; Sauvageot, N.; Crichton, G.E.; Elias, M.F. Demographic and socioeconomic disparity in nutrition: Application of a novel Correlated Component Regression approach. *BMJ Open* **2015**, *5*, e006814. [[CrossRef](#)] [[PubMed](#)]
- Koenig, M.D. Nutrient Intake During Pregnancy. *J. Obstet. Gynecol. Neonatal Nurs.* **2017**, *46*, 120–122. [[CrossRef](#)] [[PubMed](#)]
- Desai, M.; Jellyman, J.K.; Ross, M.G. Epigenomics, gestational programming and risk of metabolic syndrome. *Int. J. Obes.* **2015**, *39*, 633–641. [[CrossRef](#)] [[PubMed](#)]
- Ruchat, S.-M.; Houde, A.-A.; Voisin, G.; St-Pierre, J.; Perron, P.; Baillargeon, J.-P.; Gaudet, D.; Hivert, M.-F.; Brisson, D.; Bouchard, L. Gestational diabetes mellitus epigenetically affects genes predominantly involved in metabolic diseases. *Epigenetics* **2013**, *8*, 935–943. [[CrossRef](#)] [[PubMed](#)]
- Gagné-Ouellet, V.; Houde, A.A.; Guay, S.P. Placental lipoprotein lipase DNA methylation alterations are associated with gestational diabetes and body composition at 5 years of age. *Epigenetics* **2017**, *12*, 616–625. [[CrossRef](#)]
- Miyake, K.; Miyashita, C.; Ikeda-Araki, A.; Miura, R.; Itoh, S.; Yamazaki, K.; Kobayashi, S.; Masuda, H.; Ooka, T.; Yamagata, Z.; et al. DNA methylation of GF11 as a mediator of the association between prenatal smoking exposure and ADHD symptoms at 6 years: The Hokkaido Study on Environment and Children's Health. *Clin. Epigenet.* **2021**, *13*, 74. [[CrossRef](#)]
- Küppers, L.K.; Xu, X.; Jankipersadsing, S.A.; Vaez, A.; la Bastide-van Gemert, S.; Scholtens, S.; Nolte, I.M.; Richmond, R.C.; Relton, C.L.; Felix, J.F.; et al. DNA methylation mediates the effect of maternal smoking during pregnancy on birthweight of the offspring. *Int. J. Epidemiol.* **2015**, *44*, 1224–1237. [[CrossRef](#)]
- Sarkar, D.K.; Gangisetty, O.; Wozniak, J.R.; Eckerle, J.K.; Georgieff, M.K.; Foroud, T.M.; Wetherill, L. Persistent Changes in Stress-Regulatory Genes in Pregnant Women or Children Exposed Prenatally to Alcohol. *Alcohol. Clin. Exp. Res.* **2019**, *43*, 1887–1897. [[CrossRef](#)]
- Breton-Larrivée, M.; Elder, E.; McGraw, S. DNA methylation, environmental exposures and early embryo development. *Anim. Reprod.* **2019**, *16*, 465–474. [[CrossRef](#)]
- Urbaniak, S.K.; Boguszewska, K. 8-Oxo-7,8-Dihydro-2'-Deoxyguanosine (8-oxodG) and 8-Hydroxy-2'-Deoxyguanosine (8-OHdG) as a Potential Biomarker for Gestational Diabetes Mellitus (GDM) Development. *Molecules* **2020**, *25*, 202. [[CrossRef](#)]
- García-Sánchez, A.; Miranda-Díaz, A.G.; Cardona-Muñoz, E.G. The Role of Oxidative Stress in Physiopathology and Pharmacological Treatment with Pro- and Antioxidant Properties in Chronic Diseases. *Oxid. Med. Cell. Longev.* **2020**, *2020*, 2082145. [[CrossRef](#)] [[PubMed](#)]
- Jat, D.; Nahar, M. Oxidative stress and antioxidants: An overview. *IJARR* **2017**, *2*, 110–119.
- Venereo Gutiérrez, J.R. Daño oxidativo, radicales libres y antioxidantes. *Rev. Cuba. Med. Mil.* **2002**, *31*, 126–133.
- Savini, I.; Gasperi, V.; Catani, M.V. Oxidative Stress and Obesity. In *Obesity: A Practical Guide*; Ahmad, S.I., Imam, S.K., Eds.; Springer International Publishing: Cham, Switzerland, 2016; pp. 65–86.

15. Domej, W.; Oettl, K.; Renner, W. Oxidative stress and free radicals in COPD—Implications and relevance for treatment. *Int. J. Chronic Obstr. Pulm. Dis.* **2014**, *2014*, 1207–1224. [[CrossRef](#)] [[PubMed](#)]
16. Dennery, P.A. Effects of oxidative stress on embryonic development. *Birth Defects Res. Part C Embryo Today Rev.* **2007**, *81*, 155–162. [[CrossRef](#)] [[PubMed](#)]
17. Luo, Z.C.; Fraser, W.D.; Julien, P.; Deal, C.L.; Audibert, F.; Smith, G.N.; Xiong, X.; Walker, M. Tracing the origins of “fetal origins” of adult diseases: Programming by oxidative stress? *Med. Hypotheses* **2006**, *66*, 38–44. [[CrossRef](#)] [[PubMed](#)]
18. Cadet, J.; Wagner, J.R.; Shafirovich, V.; Geacintov, N.E. One-electron oxidation reactions of purine and pyrimidine bases in cellular DNA. *Int. J. Radiat. Biol.* **2014**, *90*, 423–432. [[CrossRef](#)]
19. Asami, S.; Manabe, H.; Miyake, J.; Tsurudome, Y.; Hirano, T.; Yamaguchi, R.; Itoh, H.; Kasai, H. Cigarette smoking induces an increase in oxidative DNA damage, 8-hydroxydeoxyguanosine, in a central site of the human lung. *Carcinogenesis* **1997**, *18*, 1763–1766. [[CrossRef](#)]
20. Thomas, M.C.; Woodward, M.; Li, Q.; Pickering, R.; Tikellis, C.; Poulter, N.; Cooper, M.E.; Marre, M.; Zoungas, S.; Chalmers, J. Relationship Between Plasma 8-OH-Deoxyguanosine and Cardiovascular Disease and Survival in Type 2 Diabetes Mellitus: Results from the ADVANCE Trial. *J. Am. Heart Assoc.* **2018**, *7*, e008226. [[CrossRef](#)]
21. Leinonen, J.; Lehtimäki, T.; Toyokuni, S.; Okada, K.; Tanaka, T.; Hiai, H.; Ochi, H.; Laippala, P.; Rantalaiho, V.; Wirta, O.; et al. New biomarker evidence of oxidative DNA damage in patients with non-insulin-dependent diabetes mellitus. *FEBS Lett.* **1997**, *417*, 150–152. [[CrossRef](#)]
22. Chuma, M.; Hige, S.; Nakanishi, M.; Ogawa, K.; Natsuzaka, M.; Yamamoto, Y.; Asaka, M. 8-Hydroxy-2'-deoxy-guanosine is a risk factor for development of hepatocellular carcinoma in patients with chronic hepatitis C virus infection. *J. Gastroenterol. Hepatol.* **2008**, *23*, 1431–1436. [[CrossRef](#)] [[PubMed](#)]
23. Erhola, M.; Toyokuni, S.; Okada, K.; Tanaka, T.; Hiai, H.; Ochi, H.; Uchida, K.; Osawa, T.; Nieminen, M.M.; Alho, H.; et al. Biomarker evidence of DNA oxidation in lung cancer patients: Association of urinary 8-hydroxy-2'-deoxyguanosine excretion with radiotherapy, chemotherapy, and response to treatment. *FEBS Lett.* **1997**, *409*, 287–291. [[CrossRef](#)]
24. Liu, Z.; Cai, Y.; He, J. High serum levels of 8-OHdG are an independent predictor of post-stroke depression in Chinese stroke survivors. *Neuropsychiatr. Dis. Treat.* **2018**, *14*, 587–596. [[CrossRef](#)] [[PubMed](#)]
25. Chen, Y.-C.; Chen, C.-M.; Liu, J.-L.; Chen, S.-T.; Cheng, M.-L.; Chiu, D.T.-Y. Oxidative markers in spontaneous intracerebral hemorrhage: Leukocyte 8-hydroxy-2'-deoxyguanosine as an independent predictor of the 30-day outcome. *J. Neurosurg.* **2011**, *115*, 1184–1190. [[CrossRef](#)] [[PubMed](#)]
26. Iida, T.; Inoue, K.; Ito, Y.; Ishikawa, H.; Kagiono, M.; Teradaira, R.; Chikamura, C.; Harada, T.; Ezoe, S.; Yatsuya, H. Comparison of urinary levels of 8-hydroxy-2'-deoxyguanosine between young females with and without depressive symptoms during different menstrual phases. *Acta Med. Okayama* **2015**, *69*, 45–50. [[CrossRef](#)] [[PubMed](#)]
27. Martinet, W.; Knaapen, M.W.; De Meyer, G.R.; Herman, A.G.; Kockx, M.M. Elevated levels of oxidative DNA damage and DNA repair enzymes in human atherosclerotic plaques. *Circulation* **2002**, *106*, 927–932. [[CrossRef](#)] [[PubMed](#)]
28. Miyamoto, M.; Kotani, K.; Ishibashi, S.; Taniguchi, N. The relationship between urinary 8-hydroxydeoxyguanosine and metabolic risk factors in asymptomatic subjects. *Med. Princ. Pract. Int. J. Kuwait Univ. Health Sci. Cent.* **2011**, *20*, 187–190. [[CrossRef](#)]
29. Satoh, M.; Ishikawa, Y.; Takahashi, Y.; Itoh, T.; Minami, Y.; Nakamura, M. Association between oxidative DNA damage and telomere shortening in circulating endothelial progenitor cells obtained from metabolic syndrome patients with coronary artery disease. *Atherosclerosis* **2008**, *198*, 347–353. [[CrossRef](#)]
30. Min, J.; Park, B.; Kim, Y.J.; Lee, H.; Ha, E.; Park, H. Effect of oxidative stress on birth sizes: Consideration of window from mid pregnancy to delivery. *Placenta* **2009**, *30*, 418–423. [[CrossRef](#)]
31. Murata, T.; Kyozuka, H.; Fukuda, T.; Endo, Y.; Kanno, A.; Yasuda, S.; Yamaguchi, A.; Sato, A.; Ogata, Y.; Shinoki, K.; et al. Urinary 8-hydroxy-2'-deoxyguanosine levels and small-for-gestational age infants: A prospective cohort study from the Japan Environment and Children's Study. *BMJ Open* **2021**, *11*, e054156. [[CrossRef](#)]
32. Yuan, Y.; Zhang, L.; Jin, L.; Liu, J.; Li, Z.; Wang, L.; Ren, A. Markers of macromolecular oxidative damage in maternal serum and risk of neural tube defects in offspring. *Free Radic. Biol. Med.* **2015**, *80*, 27–32. [[CrossRef](#)] [[PubMed](#)]
33. Hozyasz, K.K.; Chełchowska, M.; Ambroszkiewicz, J.; Gajewska, J.; Dudkiewicz, Z.; Laskowska-Klita, T. Oxidative DNA damage in mothers of children with isolated orofacial clefts. *Prz. Lek.* **2004**, *61*, 1310–1313.
34. Qiu, C.; Hevner, K.; Abetew, D.; Enquobahrie, D.A.; Williams, M.A. Oxidative DNA damage in early pregnancy and risk of gestational diabetes mellitus: A pilot study. *Clin. Biochem.* **2011**, *44*, 804–808. [[CrossRef](#)] [[PubMed](#)]
35. Gelaleti, R.B.; Damasceno, D.C.; Lima, P.H.O.; Salvadori, D.M.F.; Calderon, I.d.M.P.; Peraçoli, J.C.; Rudge, M.V.C. Oxidative DNA damage in diabetic and mild gestational hyperglycemic pregnant women. *Diabetol. Metab. Syndr.* **2015**, *7*, 1. [[CrossRef](#)] [[PubMed](#)]
36. Moreno-Fernandez, J.; Ochoa, J.J. COVID-19 during Gestation: Maternal Implications of Evoked Oxidative Stress and Iron Metabolism Impairment. *Antioxidants* **2022**, *11*, 184. [[CrossRef](#)]
37. Olorunnisola, O.; Ajayi, A.; Okeleji, L.; Abimbola, O.; Emorioloye, J. Vitamins as Antioxidants. *J. Food Sci. Nutr. Res.* **2019**, *2*, 214–235. [[CrossRef](#)]
38. Lee, B.M.; Lee, S.K.; Kim, H.S. Inhibition of oxidative DNA damage, 8-OHdG, and carbonyl contents in smokers treated with antioxidants (vitamin E, vitamin C, β -carotene and red ginseng). *Cancer Lett.* **1998**, *132*, 219–227. [[CrossRef](#)]

39. Lopez-Yañez Blanco, A.; Díaz-López, K.M.; Vilchis-Gil, J.; Diaz-Garcia, H.; Gomez-Lopez, J.; Medina-Bravo, P.; Granados-Riveron, J.T.; Gallardo, J.M.; Klünder-Klünder, M.; Sánchez-Urbina, R. Diet and Maternal Obesity Are Associated with Increased Oxidative Stress in Newborns: A Cross-Sectional Study. *Nutrients* **2022**, *14*, 746. [[CrossRef](#)]
40. Bandiera, F.C.; Pérez-Stable, E.J.; Atem, F.; Caetano, R.; Vidot, D.C.; Gellman, M.D.; Navas-Nacher, E.L.; Cai, J.; Talavera, G.; Schneiderman, N.; et al. At risk alcohol consumption with smoking by national background: Results from the Hispanic community health study/study of Latinos. *Addict. Behav.* **2019**, *99*, 106087. [[CrossRef](#)]
41. Castilla-Peon, M.F.; Bravo, P.G.M.; Sánchez-Urbina, R.; Gallardo-Montoya, J.M.; Soriano-López, L.C.; Cruz, F.M.C. Diabetes and obesity during pregnancy are associated with oxidative stress genotoxicity in newborns. *J. Perinat. Med.* **2019**, *47*, 347–353. [[CrossRef](#)]
42. *Institute of Medicine (US) Standing Committee on the Scientific Evaluation of Dietary Reference Intakes and Its Panel on Folate, Other B Vitamins, and Choline*; National Academy of Sciences: Washington, DC, USA, 1998.
43. Toescu, V.; Nuttall, S.L.; Martin, U.; Kendall, M.J.; Dunne, F. Oxidative stress and normal pregnancy. *Clin. Endocrinol.* **2002**, *57*, 609–613. [[CrossRef](#)] [[PubMed](#)]
44. Toboła-Wróbel, K.; Pietryga, M.; Dydowicz, P.; Napierała, M.; Brązert, J.; Florek, E. Association of Oxidative Stress on Pregnancy. *Oxid. Med. Cell. Longev.* **2020**, *2020*, 6398520. [[CrossRef](#)] [[PubMed](#)]
45. Mistry, H.D.; Williams, P.J. The importance of antioxidant micronutrients in pregnancy. *Oxid. Med. Cell. Longev.* **2011**, *2011*, 841749. [[CrossRef](#)] [[PubMed](#)]
46. Ebina, S.; Chiba, T.; Ozaki, T.; Kashiwakura, I. Relationship between 8-hydroxydeoxyguanosine levels in placental/umbilical cord blood and maternal/neonatal obstetric factors. *Exp. Ther. Med.* **2012**, *4*, 387–390. [[CrossRef](#)] [[PubMed](#)]
47. Stadem, P.S.; Hilgers, M.V.; Bengo, D.; Cusick, S.E.; Ndidde, S.; Slusher, T.M.; Lund, T.C. Markers of oxidative stress in umbilical cord blood from G6PD deficient African newborns. *PLoS ONE* **2017**, *12*, e0172980. [[CrossRef](#)] [[PubMed](#)]
48. Seven, A.; Güzel, S.; Aslan, M.; Hamuryudan, V. Lipid, protein, DNA oxidation and antioxidant status in rheumatoid arthritis. *Clin. Biochem.* **2008**, *41*, 538–543. [[CrossRef](#)]
49. Gallardo, J.M.; Gómez-López, J.; Medina-Bravo, P.; Juárez-Sánchez, F.; Contreras-Ramos, A.; Galicia-Esquivel, M.; Sánchez-Urbina, R.; Klünder-Klünder, M. Maternal obesity increases oxidative stress in the newborn. *Obesity* **2015**, *23*, 1650–1654. [[CrossRef](#)]
50. Cooke, M.S.; Evans, M.D.; Dizdaroglu, M.; Lunec, J. Oxidative DNA damage: Mechanisms, mutation, and disease. *FASEB J. Off. Publ. Fed. Am. Soc. Exp. Biol.* **2003**, *17*, 1195–1214. [[CrossRef](#)]
51. Al-Aubaidy, H.A.; Jelinek, H.F. Oxidative DNA damage and obesity in type 2 diabetes mellitus. *Eur. J. Endocrinol.* **2011**, *164*, 899–904. [[CrossRef](#)]
52. Schulpis, K.H.; Lazaropoulou, C.; Vlachos, G.D.; Partsinevelos, G.A.; Michalakakou, K.; Gavriili, S.; Gounaris, A.; Antsaklis, A.; Papassotiropoulou, I. Maternal-neonatal 8-hydroxy-deoxyguanosine serum concentrations as an index of DNA oxidation in association with the mode of labour and delivery. *Acta Obstet. Gynecol. Scand.* **2007**, *86*, 320–326. [[CrossRef](#)]
53. Fukushima, K.; Murata, M.; Tsukimori, K.; Eisuke, K.; Wake, N. 8-Hydroxy-2-deoxyguanosine staining in placenta is associated with maternal serum uric acid levels and gestational age at diagnosis in pre-eclampsia. *Am. J. Hypertens.* **2011**, *24*, 829–834. [[CrossRef](#)] [[PubMed](#)]
54. Maccani, J.Z.; Maccani, M.A. Altered placental DNA methylation patterns associated with maternal smoking: Current perspectives. *Adv. Genom. Genet.* **2015**, *2015*, 205–214. [[CrossRef](#)] [[PubMed](#)]
55. Rossner, P., Jr.; Milcova, A.; Libalova, H.; Novakova, Z.; Topinka, J.; Balascak, I.; Sram, R.J. Biomarkers of exposure to tobacco smoke and environmental pollutants in mothers and their transplacental transfer to the fetus. Part II. Oxidative damage. *Mutat. Res.* **2009**, *669*, 20–26. [[CrossRef](#)] [[PubMed](#)]
56. Al-Gubory, K.H. Maternal Nutrition, Oxidative Stress and Prenatal Developmental Outcomes. In *Studies on Women's Health*; Agarwal, A., Aziz, N., Rizk, B., Eds.; Humana Press: Totowa, NJ, USA, 2013; pp. 1–31.
57. Boden, G.; Homko, C.; Barrero, C.A.; Stein, T.P.; Chen, X.; Cheung, P.; Fecchio, C.; Koller, S.; Merali, S. Excessive caloric intake acutely causes oxidative stress, GLUT4 carbonylation, and insulin resistance in healthy men. *Sci. Transl. Med.* **2015**, *7*, 304re7. [[CrossRef](#)]
58. Fischer-Nielsen, A.; Jeding, I.B.; Loft, S. Radiation-induced formation of 8-hydroxy-2'-deoxyguanosine and its prevention by scavengers. *Carcinogenesis* **1994**, *15*, 1609–1612. [[CrossRef](#)]
59. Abu-Shakra, A.; Zeiger, E. Formation of 8-hydroxy-2'-deoxyguanosine following treatment of 2'-deoxyguanosine or DNA by hydrogen peroxide or glutathione. *Mutat. Res.* **1997**, *390*, 45–50. [[CrossRef](#)]
60. Block, G.; Wakimoto, P.; Jensen, C.; Mandel, S.; Green, R.R. Validation of a food frequency questionnaire for Hispanics. *Prev. Chronic Dis.* **2006**, *3*, A77.
61. Terminel-Zaragoza, R.; Vega-López, S.; Ulloa-Mercado, G.; Serna-Gutiérrez, A.; Gortáres-Moroyoqui, P.; Díaz, L.; Rentería-Mexía, A. Reproducibility and validity of a food frequency questionnaire to assess cardiovascular health-related food intake among Mexican adolescents. *J. Nutr. Sci.* **2022**, *11*, e3. [[CrossRef](#)]
62. Tamae, K.; Kawai, K.; Yamasaki, S.; Kawanami, K.; Ikeda, M.; Takahashi, K.; Miyamoto, T.; Kato, N.; Kasai, H. Effect of age, smoking and other lifestyle factors on urinary 7-methylguanine and 8-hydroxydeoxyguanosine. *Cancer Sci.* **2009**, *100*, 715–721. [[CrossRef](#)]

63. Guo, X.; Cui, H.; Zhang, H.; Guan, X.; Zhang, Z.; Jia, C.; Wu, J.; Yang, H.; Qiu, W.; Zhang, C.; et al. Protective Effect of Folic Acid on Oxidative DNA Damage: A Randomized, Double-Blind, and Placebo Controlled Clinical Trial. *Medicine* **2015**, *94*, e1872. [[CrossRef](#)]
64. Daube, H.; Scherer, G.; Riedel, K.; Ruppert, T.; Tricker, A.R.; Rosenbaum, P.; Adlkofer, F. DNA adducts in human placenta in relation to tobacco smoke exposure and plasma antioxidant status. *J. Cancer Res. Clin. Oncol.* **1997**, *123*, 141–151. [[CrossRef](#)] [[PubMed](#)]
65. Kaur, J.; Politis, C.; Jacobs, R. Salivary 8-hydroxy-2-deoxyguanosine, malondialdehyde, vitamin C, and vitamin E in oral pre-cancer and cancer: Diagnostic value and free radical mechanism of action. *Clin. Oral Investig.* **2016**, *20*, 315–319. [[CrossRef](#)] [[PubMed](#)]
66. Huang, H.Y.; Helzlsouer, K.J.; Appel, L.J. The effects of vitamin C and vitamin E on oxidative DNA damage: Results from a randomized controlled trial. *Cancer Epidemiol. Biomark. Prev. A Publ. Am. Assoc. Cancer Res. Cosponsored Am. Soc. Prev. Oncol.* **2000**, *9*, 647–652.
67. Tarng, D.-C.; Liu, T.-Y.; Huang, T.-P. Protective effect of vitamin C on 8-hydroxy-2'-deoxyguanosine level in peripheral blood lymphocytes of chronic hemodialysis patients. *Kidney Int.* **2004**, *66*, 820–831. [[CrossRef](#)]
68. Murata, M.; Kawanishi, S. Oxidative DNA Damage by Vitamin A and Its Derivative via Superoxide Generation. *J. Biol. Chem.* **2000**, *275*, 2003–2008. [[CrossRef](#)]
69. Balmer, J.E.; Blomhoff, R. Gene expression regulation by retinoic acid. *J. Lipid Res.* **2002**, *43*, 1773–1808. [[CrossRef](#)]
70. Olsen, T.; Blomhoff, R. Retinol, Retinoic Acid, and Retinol-Binding Protein 4 are Differentially Associated with Cardiovascular Disease, Type 2 Diabetes, and Obesity: An Overview of Human Studies. *Adv. Nutr.* **2020**, *11*, 644–666. [[CrossRef](#)]
71. Graham, T.E.; Yang, Q.; Blüher, M.; Hammarstedt, A.; Ciaraldi, T.P.; Henry, R.R.; Wason, C.J.; Oberbach, A.; Jansson, P.-A.; Smith, U.; et al. Retinol-Binding Protein 4 and Insulin Resistance in Lean, Obese, and Diabetic Subjects. *N. Engl. J. Med.* **2006**, *354*, 2552–2563. [[CrossRef](#)]
72. Padayatty, S.J.; Levine, M. Antioxidant supplements and cardiovascular disease in men. *JAMA* **2009**, *301*, 1336. [[CrossRef](#)]
73. Coulter, I.D.; Hardy, M.L.; Morton, S.C.; Hilton, L.G.; Tu, W.; Valentine, D.; Shekelle, P.G. Antioxidants Vitamin C and Vitamin E for the Prevention and Treatment of Cancer. *J. Gen. Intern. Med.* **2006**, *21*, 735–744. [[CrossRef](#)]
74. Deicher, R.; Hörl, W.H. Vitamin C in chronic kidney disease and hemodialysis patients. *Kidney Blood Press. Res.* **2003**, *26*, 100–106. [[CrossRef](#)] [[PubMed](#)]
75. Rezaei, Y.; Khademvatani, K.; Rahimi, B.; Khoshfetrat, M.; Arjmand, N.; Seyyed-Mohammadzad, M.-H. Short-Term High-Dose Vitamin E to Prevent Contrast Medium-Induced Acute Kidney Injury in Patients with Chronic Kidney Disease Undergoing Elective Coronary Angiography: A Randomized Placebo-Controlled Trial. *J. Am. Heart Assoc.* **2016**, *5*, e002919. [[CrossRef](#)] [[PubMed](#)]
76. Garcia-Diaz, D.F.; Lopez-Legarrea, P.; Quintero, P.; Martinez, J.A. Vitamin C in the treatment and/or prevention of obesity. *J. Nutr. Sci. Vitaminol.* **2014**, *60*, 367–379. [[CrossRef](#)] [[PubMed](#)]
77. Hendarto, A.; Alhadar, A.K.; Sjarif, D.R. The Effect of Vitamin E Supplementation on Lipid Profiles and Adiponectin Levels in Obese Adolescents: A Randomized Controlled Trial. *Acta Med. Indones.* **2019**, *51*, 110–116.
78. Garcia-Bailo, B.; El-Soheby, A.; Haddad, P.S.; Arora, P.; Benzaied, F.; Karmali, M.; Badawi, A. Vitamins D, C, and E in the prevention of type 2 diabetes mellitus: Modulation of inflammation and oxidative stress. *Biol. Targets Ther.* **2011**, *5*, 7–19. [[CrossRef](#)]
79. Ismail, N.M.; Harun, A.; Yusof, A.A.; Zaiton, Z.; Marzuki, A. Role of vitamin e on oxidative stress in smokers. *Malays. J. Med. Sci.* **2002**, *9*, 34–42.
80. Kaźmierczak-Barańska, J.; Boguszewska, K.; Adamus-Grabicka, A.; Karwowski, B.T. Two Faces of Vitamin C-Antioxidative and Pro-Oxidative Agent. *Nutrients* **2020**, *12*, 1501. [[CrossRef](#)]
81. Podmore, I.D.; Griffiths, H.R.; Herbert, K.E.; Mistry, N.; Mistry, P.; Lunec, J. Vitamin C exhibits pro-oxidant properties. *Nature* **1998**, *392*, 559. [[CrossRef](#)]
82. Pearson, P.; Lewis, S.A.; Britton, J.; Young, I.S.; Fogarty, A. The pro-oxidant activity of high-dose vitamin E supplements in vivo. *BioDrugs Clin. Immunother. Biopharm. Gene Ther.* **2006**, *20*, 271–273. [[CrossRef](#)]
83. Weinberg, R.B.; VanderWerken, B.S.; Anderson, R.A.; Stegner, J.E.; Thomas, M.J. Pro-Oxidant Effect of Vitamin E in Cigarette Smokers Consuming a High Polyunsaturated Fat Diet. *Arterioscler. Thromb. Vasc. Biol.* **2001**, *21*, 1029–1033. [[CrossRef](#)]
84. Rendón-Ramírez, A.; Maldonado-Vega, M.; Quintanar-Escorza, M.; Hernández, G.; Arévalo, B.; Zentella-Dehesa, A.; Calderón-Salinas, J.-V. Effect of vitamin E and C supplementation on oxidative damage and total antioxidant capacity in lead-exposed workers. *Environ. Toxicol. Pharmacol.* **2014**, *37*, 45–54. [[CrossRef](#)] [[PubMed](#)]
85. Prajapat, R.; Bhattacharya, I. Effect of Vitamin E and C Supplementation on Oxidative Stress in Diabetic Patients. *Adv. Diabetes Metab.* **2017**, *5*, 39–42. [[CrossRef](#)]
86. Brown, K.M.; Morrice, P.C.; Duthie, G.G. Erythrocyte vitamin E and plasma ascorbate concentrations in relation to erythrocyte peroxidation in smokers and nonsmokers: Dose response to vitamin E supplementation. *Am. J. Clin. Nutr.* **1997**, *65*, 496–502. [[CrossRef](#)] [[PubMed](#)]
87. Bader, N.; Bosa-Westphal, A.; Koch, A.; Mueller, M.J. Influence of vitamin C and E supplementation on oxidative stress induced by hyperbaric oxygen in healthy men. *Ann. Nutr. Metab.* **2006**, *50*, 173–176. [[CrossRef](#)] [[PubMed](#)]
88. Bader, N.; Bosa-Westphal, A.; Koch, A.; Rimbach, G.; Weimann, A.; Poulsen, H.E.; Müller, M.J. Effect of hyperbaric oxygen and vitamin C and E supplementation on biomarkers of oxidative stress in healthy men. *Br. J. Nutr.* **2007**, *98*, 826–833. [[CrossRef](#)]

89. Lutsenko, E.A.; Cárcamo, J.M.; Golde, D.W. Vitamin C prevents DNA mutation induced by oxidative stress. *J. Biol. Chem.* **2002**, *277*, 16895–16899. [[CrossRef](#)]
90. Guarnieri, S.; Loft, S.; Riso, P.; Porrini, M.; Risom, L.; Poulsen, H.E.; Dragsted, L.O.; Møller, P. DNA repair phenotype and dietary antioxidant supplementation. *Br. J. Nutr.* **2008**, *99*, 1018–1024. [[CrossRef](#)]
91. Bobo, J.K.; Husten, C. Sociocultural influences on smoking and drinking. *Alcohol Res. Health J. Natl. Inst. Alcohol Abus. Alcohol.* **2000**, *24*, 225–232.
92. McEvoy, C.T.; Spindel, E.R. Pulmonary Effects of Maternal Smoking on the Fetus and Child: Effects on Lung Development, Respiratory Morbidities, and Life Long Lung Health. *Paediatr. Respir. Rev.* **2017**, *21*, 27–33. [[CrossRef](#)]
93. Corrales-Gutierrez, I.; Baena-Antequera, F.; Gomez-Baya, D.; Leon-Larios, F.; Mendoza, R. Relationship between Eating Habits, Physical Activity and Tobacco and Alcohol Use in Pregnant Women: Sociodemographic Inequalities. *Nutrients* **2022**, *14*, 557. [[CrossRef](#)]
94. Vadhanam, M.V.; Thaiparambil, J.; Gairola, C.G.; Gupta, R.C. Oxidative DNA Adducts Detected in Vitro from Redox Activity of Cigarette Smoke Constituents. *Chem. Res. Toxicol.* **2012**, *25*, 2499–2504. [[CrossRef](#)] [[PubMed](#)]
95. Pryor, W.A. Cigarette smoke radicals and the role of free radicals in chemical carcinogenicity. *Environ. Health Perspect.* **1997**, *105* (Suppl. S4), 875–882. [[CrossRef](#)] [[PubMed](#)]
96. Cantin, A.M. Cellular Response to Cigarette Smoke and Oxidants. *Proc. Am. Thorac. Soc.* **2010**, *7*, 368–375. [[CrossRef](#)] [[PubMed](#)]
97. Lobo, V.; Patil, A.; Phatak, A.; Chandra, N. Free radicals, antioxidants and functional foods: Impact on human health. *Pharm. Rev.* **2010**, *4*, 118–126. [[CrossRef](#)] [[PubMed](#)]
98. Cao, C.; Lai, T.; Li, M.; Zhou, H.; Lv, D.; Deng, Z.; Ying, S.; Chen, Z.; Li, W.; Shen, H. Smoking-promoted oxidative DNA damage response is highly correlated to lung carcinogenesis. *Oncotarget* **2016**, *7*, 18919–18926. [[CrossRef](#)] [[PubMed](#)]
99. Jha, P. Avoidable global cancer deaths and total deaths from smoking. *Nat. Rev. Cancer* **2009**, *9*, 655–664. [[CrossRef](#)]
100. Nabet, C.; Ancel, P.-Y.; Burguet, A.; Kaminski, M. Smoking during pregnancy and preterm birth according to obstetric history: French national perinatal surveys. *Paediatr. Perinat. Epidemiol.* **2005**, *19*, 88–96. [[CrossRef](#)]
101. Kyrklund-Blomberg, N.B.; Granath, F.; Cnattingius, S. Maternal smoking and causes of very preterm birth. *Acta Obstet. Gynecol. Scand.* **2005**, *84*, 572–577. [[CrossRef](#)]
102. Steyn, K.; de Wet, T.; Saloojee, Y.; Nel, H.; Yach, D. The influence of maternal cigarette smoking, snuff use and passive smoking on pregnancy outcomes: The Birth to Ten Study. *Paediatr. Perinat. Epidemiol.* **2006**, *20*, 90–99. [[CrossRef](#)]
103. Alverson, C.J.; Strickland, M.J.; Gilboa, S.M.; Correa, A. Maternal smoking and congenital heart defects in the Baltimore-Washington Infant Study. *Pediatrics* **2011**, *127*, e647–e653. [[CrossRef](#)]
104. García-Villarino, M.; Fernández-Iglesias, R. Prenatal Exposure to Cigarette Smoke and Anogenital Distance at 4 Years in the INMA-Asturias Cohort. *Int. J. Environ. Res. Public Health* **2021**, *18*, 4774. [[CrossRef](#)] [[PubMed](#)]
105. Zlotkowska, R.; Zejda, J.E. Fetal and postnatal exposure to tobacco smoke and respiratory health in children. *Eur. J. Epidemiol.* **2005**, *20*, 719–727. [[CrossRef](#)] [[PubMed](#)]
106. Lannerö, E.; Wickman, M.; Pershagen, G.; Nordvall, L. Maternal smoking during pregnancy increases the risk of recurrent wheezing during the first years of life (BAMSE). *Respir. Res.* **2006**, *7*, 3. [[CrossRef](#)] [[PubMed](#)]
107. Bjerg, A.; Hedman, L.; Perzanowski, M.; Lundbäck, B.; Rönmark, E. A strong synergism of low birth weight and prenatal smoking on asthma in schoolchildren. *Pediatrics* **2011**, *127*, e905–e912. [[CrossRef](#)] [[PubMed](#)]
108. Taylor, B.; Wadsworth, J. Maternal smoking during pregnancy and lower respiratory tract illness in early life. *Arch. Dis. Child.* **1987**, *62*, 786–791. [[CrossRef](#)]
109. Ekblad, M.; Lehtonen, L.; Korkeila, J.; Gissler, M. Maternal Smoking During Pregnancy and the Risk of Psychiatric Morbidity in Singleton Sibling Pairs. *Nicotine Tob. Res. Off. J. Soc. Res. Nicotine Tob.* **2017**, *19*, 597–604. [[CrossRef](#)]
110. Sourander, A.; Sucksdorff, M.; Chudal, R.; Surcel, H.M.; Hinkka-Yli-Salomäki, S.; Gyllenberg, D.; Cheslack-Postava, K.; Brown, A.S. Prenatal Cotinine Levels and ADHD Among Offspring. *Pediatrics* **2019**, *143*, e20183144. [[CrossRef](#)]
111. Kovess, V.; Keyes, K.M.; Hamilton, A.; Pez, O.; Bitfoi, A.; Koç, C.; Goelitz, D.; Kuijpers, R.; Lesinskiene, S.; Mihova, Z.; et al. Maternal smoking and offspring inattention and hyperactivity: Results from a cross-national European survey. *Eur. Child Adolesc. Psychiatry* **2015**, *24*, 919–929. [[CrossRef](#)]
112. Brannigan, R.; Tanskanen, A.; Huttunen, M.O.; Cannon, M.; Leacy, F.P.; Clarke, M.C. Maternal smoking during pregnancy and offspring psychiatric disorder: A longitudinal birth cohort study. *Soc. Psychiatry Psychiatr. Epidemiol.* **2022**, *57*, 595–600. [[CrossRef](#)]
113. Krall, E.A.; Dawson-Hughes, B. Smoking increases bone loss and decreases intestinal calcium absorption. *J. Bone Miner. Res. Off. J. Am. Soc. Bone Miner. Res.* **1999**, *14*, 215–220. [[CrossRef](#)]
114. Linnell, J.C.; Smith, A.D.; Smith, C.L.; Wilson, J.; Matthews, D.M. Effects of smoking on metabolism and excretion of vitamin B12. *Br. Med. J.* **1968**, *2*, 215–216. [[CrossRef](#)] [[PubMed](#)]
115. Brot, C.; Jorgensen, N.R.; Sorensen, O.H. The influence of smoking on vitamin D status and calcium metabolism. *Eur. J. Clin. Nutr.* **1999**, *53*, 920–926. [[CrossRef](#)] [[PubMed](#)]
116. Sealey, W.M.; Teague, A.M.; Stratton, S.L.; Mock, D.M. Smoking accelerates biotin catabolism in women. *Am. J. Clin. Nutr.* **2004**, *80*, 932–935. [[CrossRef](#)] [[PubMed](#)]
117. Bruno, R.S.; Ramakrishnan, R.; Montine, T.J.; Bray, T.M.; Traber, M.G. α -Tocopherol disappearance is faster in cigarette smokers and is inversely related to their ascorbic acid status. *Am. J. Clin. Nutr.* **2005**, *81*, 95–103. [[CrossRef](#)] [[PubMed](#)]