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Oxidative Stress Trajectories during Lifespan: The Possible Mediation Role of Hormones in Redox Imbalance and Aging

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Abstract: Aging, a natural multifactorial process, increases Oxidative Stress (OS) and inflammatory responses. Sexual hormones could upregulate OS during lifespan, with opposite systemic effects: anti-oxidant protection and cellular pro-oxidant toxicity. Hormonal changes are crucial phases in human growth and aging, but their mediating role on OS is still incomplete. The main purpose of this work was to analyze the trend of OS during the lifespan and, in particular, during puberty and menopause. Data from standardized questionnaires and biological OS measurements (15-F2t-Isop) of 815 subjects (7–60 years old) from five previous studies (2009–2015) were analyzed. The age variable was categorized into two hormonal age windows: puberty and menopause. A regression model was performed to assess the association between 15-F2t-Isop and the hormonal age window, sex, weight, and smoking habits. The results showed a significant V-shape decrease of OS levels both during puberty [OR = −0.06 95% CI −0.07–−0.04, $p = 0.41$] and in menopause [OR = −1.01 95% CI −1.5–−0.5, $p < 0.001$], but only in females. Our results support the view that hormones, and specifically estrogen, could modulate OS, especially during puberty and menopause. The V-shape decreasing trend of OS may be related to intrinsic characteristics of estrogen, which is able to modulate and upregulate OS pro- and anti-oxidant mechanisms.

Keywords: oxidative stress; lifespan trend; hormonal windows; puberty and menopause; OS upregulation

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1. Introduction

Aging is a natural and multifactorial process determined by both genetic and environmental factors that begins even before birth [1]. One of the key characteristics of aging is a steady increase in Oxidative Stress (OS) and inflammatory responses. These phenomena are associated with an enhancement of cellular senescence and organ dysfunction resulting, in turn, in a gradual decline in human physical and mental faculties. OS, indeed, can influence and modify the homeostatic balances and significantly alter cellular responses to injuries [2]. Since peri-conceptional oxidative imbalance can even affect fetal development, as well as later health status, we can state that the aging process begins before birth [3]. Indeed, OS occurs clearly during the early stages of pregnancy and then continues during the postnatal period and throughout the lifespan.

To date, several theories have been proposed to explain the aging process, but none of them have yet to be completely accepted by the scientific community. Among these, the "free radical theory", also known as the "Mitochondrial Free Radical Theory of Aging" (MFRTA), has been, and continues to be, the basis of extensive research on the interplay between OS and the onset of degenerative conditions associated with the aging process [4]. MFRTA proposes that aging is caused by general and prolonged damage to macromolecules caused by Reactive Oxygen Species (ROS) produced in mitochondria, through a vicious cycle in which ROS damage to mitochondrial constituents lead to further generation of other ROS [5]. The strengths of this theory are the following: (i) a strong correlation between

chronological age and the levels of both ROS generation and oxidative damage, (ii) the gradual loss of mitochondrial functions during aging, (iii) the enhancement in ROS production due to the inhibition of mitochondrial functions, and (iv) the association between a severe increase of OS and several age-dependent conditions and diseases [6]. Partially contrasting with the MFRTA, evidence emerged in recent years which hypothesized that ROS may also be potentially lifespan-promoting, signalling molecules transducing messages from the mitochondria to other organelles in the cell [7,8]. According to this theory, low-level oxidative damage can culminate in increased stress resistance and, ultimately, in longevity. This adaptive response is marked by biphasic dose–response patterns to the ROS-related stress in mitochondria and can be considered a case of hormesis [9–11].

Among factors able to upregulate and modulate OS during the lifespan, an important role is played by sexual hormones. These molecules can have opposite and diverse systemic effects: they can be involved in cellular protection, via their anti-oxidant properties [12,13], and in cellular toxicity, via their pro-oxidant properties [14–17]. Sexual hormones are produced throughout the lifespan of an organism, including during prenatal development, puberty, and aging [18,19].

In post-menopausal women, the progressive depletion of estrogen and its protective effect, combined with deficient antioxidant defence, can lead to a pronounced redox imbalance, in addition to the known symptoms [20,21]. Indeed, compared to pre-menopausal women, post-menopausal women have higher levels of lipoperoxide [22], pro-inflammatory cytokines [23] and, in general, higher levels of OS biomarkers [24]. Unfortunately, while many studies have focused on the relationship between sex hormones and OS during the menopausal window, only a few studies have analyzed the same relationship during childhood and adolescence. Specifically, even puberty is a crucial phase in human growth and development, and the possible positive or negative mediating roles of sex hormones on OS during this stage is still incomplete.

In this perspective, the main purpose of this work was to analyze the following: (i) the trend of OS during a lifespan, from age seven to sixty years old; (ii) the peculiar trend of OS during two delicate and sensitive hormonal windows, namely, puberty and menopause. The introduction briefly places the study in its broad context and highlights why it is important. It defines the purpose of the work and its significance. The current state of the research field is carefully reviewed and key publications cited. Controversial and diverging hypotheses are highlighted when necessary. Finally, the main aim of the work and the principal conclusions are highlighted.

2. Materials and Methods

2.1. Epidemiological Sample

The epidemiological sample for the present study was constituted by a combination of subjects enrolled in 5 previous studies, carried out between 2009 and 2015 [25–29]. The general purpose of the relevant projects was to investigate OS levels in humans, according to two different expositive approaches, namely working and living environments. All the studies were characterized by a similar protocol, requiring the following: (i) a standardized questionnaire, focusing on personal characteristics and lifestyle habits; (ii) a spot urine sample for the OS biomarker analyses. In studies enrolling workers, only healthy white-collar subjects, and not occupationally exposed subjects, were included in the present study.

2.2. OS Biological Measurements

All the subjects were asked to give a spot of urine to measure OS stress levels through a well-known biomarker, namely, 15-F2t-isoprostane (15-F2t-Isop).

Concentrations of urinary OS biomarkers proposed as an effective biomarker to survey populations exposed to xenobiotics, such as particulates, and more information on the 15-F2t-Isop, can be found elsewhere [30,31]. The biomarker, 15-F2t-Isop, is relatively stable in urine [32] and can be measured by two main analytical approaches: mass-based techniques (Gas Chromatography (GC) or Liquid Chromatography (LC)) and immunolog-

ical techniques. Even if Gas Chromatography–Mass Spectrometry (GC–MS) is the gold standard, immunological techniques are widely used to measure 15-F2t-Isop, because these assays are cost-effective, rapid, and easy to quantify. In all the biological samples, 15-F2t-Isop was analyzed through a competitive enzyme-linked immunoassay (ELISA) (EA85, Oxford biomedical, Oxford, MI, USA), following the manufacturer's instructions. To normalize the excretion rate of 15-F2t-IsoP, an aliquot of fresh urine was used to quantify the concentration of creatinine (CREA) by means of the kinetic Jaffè procedure.

Our previous papers report all the details of this procedure [27,33,34].

2.3. Confounding Factors

To control the most important confounding factors of OS imbalance, we evaluated the living environment, the Body Mass Index (BMI), and smoking habits.

- **BMI:** self-reported height and weight were used to calculate BMI ([Weight (kg)]/[(Height (m))^2]) and the epidemiological sample was classified as Underweight, Normal, Overweight, or Obese according to the reference values provided by the OMS for the different age groups [35]. In the present study, we grouped the subjects as Overweight or Obese (OwO) and not overweight or obese (not OwO).
- **Smoking habit:** subjects were asked to indicate whether they were exposed or not to tobacco smoke and, consequently, each subject was categorized as a non-smoker or an active smoker.

2.4. Statistical Analyses

The demographic, personal and biological characteristics and measurements of the subjects were summarized as absolute and relative frequencies for categorical variables and as mean (±SD) for continuous variables. The age variable was categorized in two different hormonal windows: puberty [36] (>10 years old = pre-puberty/11–14 years old = puberty/15–20 years old = post-puberty) and menopause [37] (39–45 years old = pre-menopause/46–50 years old = early menopause/50–60 years old = late menopause). Due to the hierarchical structure of our data (815 subjects from 5 different studies), a regression model was performed to assess the association between 15-F2t-Isop, as the dependent variable, linear and categorized age, sex, being OwO, and smoking habit, as independent variables. All the models were performed in the sample and then stratified for sex and age class. The results were reported as B coefficients (B) with 95% Confidence Intervals (CIs). All analyses were carried out using the STATA 16.1 software (Stata Corp LLC: College Station, TX, USA).

3. Results

Table 1 reports demographic, individual and biological characteristics of all the epidemiological samples and of sub-groups, according to the two hormonal windows of puberty and menopause.

Eight Hundred and Fifteen subjects, aged from 7 to 60 years of age were analyzed, of whom 49.2% were males. Thirty-two percent of the whole sample were classified as being OwO, of whom 39.6% were male and 24.6% female. The tobacco smoking habit, according to Italian trends [38], showed a prevalence of around 19%, higher in males. Finally, the OS level, quantified through 15-F2t-Isop, is reported in Table 1, following the same classification employed above. Figure 1 shows the increasing trend observed during the lifespans of all enrolled subjects.

A regression model was performed, with 15-F2t-Isop as the dependent variable, and age, sex, being OwO, and smoking habits, as the independent variables (Table 2). In the whole sample, the model showed a significant association with sex [B = 1.2 95% CI 0.81–1.6, $p < 0.001$] and age [B = 0.02 95% CI 0.02–0.04, $p < 0.001$], respectively. Instead, OwO and smoke did not show significant associations. The same model, stratified by means of sex, showed a statistical association between OS and age, but only in females [B = 0.06 95% CI 0.05–0.08, $p < 0.001$].

Table 1. Descriptive of the characteristics of all the samples and sub-grouped into hormonal windows (puberty and menopause).

	All sample (N = 815)	**Puberty (N = 290) Pre-Puberty (N = 75) Puberty (N = 159) Post-Puberty (N = 56)**		**Menopause (N = 375) Pre-Menopause (N = 125) Early Menopause (N = 116) Late Menopause (N = 134)**	
Gender (%)	Male: 401 (49.2%) Female: 414 (50.8%)	Pre-puberty	Male: 43 (57.3%) Female: 32 (42.7%)	Pre-menopause	Male: 53 (42.4%) Female: 72 (57.6%)
		Puberty	Male: 80 (50.3%) Female: 79 (49.7%)	Early menopause	Male: 45 (38.8%) Female: 71 (61.2%)
		Post-puberty	Male: 33 (58.9%) Female: 23 (41.1%)	Late menopause	Male: 61 (45.5%) Female: 73(54.6%)
Age (years) [Mean ± S.D.]	32.6 ± 0.6 Male: 30.8 ± 0.8 Female: 34.2 ± 0.8	Pre-puberty	8.9 ± 0.1	Pre-menopause	41.8 ± 0.1
		Puberty	12.8 ± 0.08	Early menopause	47.7 ± 0.1
		Post-puberty	17.7 ± 0.1	Late menopause	55.1 ± 0.2
OwO (%)	261 (32%) Male: 159 (39.6%) Female: 102 (24.6%)	Pre-puberty	Male: 8 (18.6%) Female: 6 (18.7%)	Pre-menopause	Male: 14 (26.4%) Female: 12 (16.6%)
		Puberty	Male: 17 (21.2%) Female: 11 (13.9%)	Early menopause	Male: 11 (24.4%) Female: 26 (36.6%)
		Post-puberty	Male: 8 (24.2%) Female: 5 (21.7%)	Late menopause	Male: 16 (26.2%) Female: 23 (31.5%)
Tobacco Smoke (%)	No: 654 (80.2%) Active: 161 (19.8%) *[85 Male/76 Female]*	Pre-puberty	No: 75 (100%) Active: 0	Pre-menopause	No: 83 (66.4%) Active: 42 (33.6%) *[21 Male/21 Female]*
		Puberty	No: 156 (98.1%) Active: 3 (1.9%) *[2 Male/1 Female]*	Early menopause	No: 90 (77.6%) Active: 26 (22.4%) *[13 Male/13 Female]*
		Post-puberty	No: 43 (76.8%) Active: 13 (23.2%) *[9 Male/4 Female]*	Late menopause	No: 99 (73.9%) Active: 35 (26.1%) *[18 Male/17 Female]*
15-F2t-Isop [ng/mg$_{CREA}$] [mean ± S.D./ min-max]	4.6 ± 5.2 [0.1–41.2] Male: 3.6 ± 4 [0.1–39.8] Female: 5.5 ± 5.9 [0.2–42.3]	Pre-puberty	5.5 ± 0.9 Male: 3.9 ± 4 [0.9–17.7] Female: 6.3 ± 5.7 [1–22.4]	Pre-menopause	5.8 ± 5.7 Male: 3.8 ± 4.9 [0.2–28.9] Female: 7.2 ± 5.8 [1.2–28.4]
		Puberty	4.8 ± 0.4 Male: 4.5 ± 2 [0.9–9.1] Female: 3.4 ± 1.9 [0.5–9.5]	Early menopause	4.1 ± 3.2 Male: 2.5 ± 1.4 [0.6–8.4] Female: 5 ± 3.6 [0.2–14.7]
		Post-puberty	5.1 ± 0.8 Male: 4.8 ± 4.9 [0.9–22.1] Female: 6.7 ± 6.2 [1.1–24.1]	Late menopause	5.2 ± 5 Male: 2.9 ± 1.9 [0.3–8.9] Female: 7.1 ± 5.9 [1.1–27.2]

Since the purpose of this work was to analyze the possible mediator role of hormones on redox modulation, additional statistical analyses were performed focusing on the two hormonal windows previously mentioned.

In subjects in the pubertal age group, the regression model did not show any significant association, while it revealed a positive association in the female subgroup [B= −0.06 95% CI −0.07–−0.04, p = 0.41]. To deepen the insight into this association, the sample was

stratified in terms of sex (Figure 2). The pairwise comparisons of means with equal variance (Table 3) showed a significant V-shape decrease of OS levels, but only in females (Tukey's test 1 (pre-puberty) vs. 2 (puberty): −2.8, $p < 0.001$ 95% CI [−1.1/−0.4]; 2 (puberty) vs. 3 (post-puberty): 2.4, $p = 0.01$ 95% CI [0.5/4.4]).

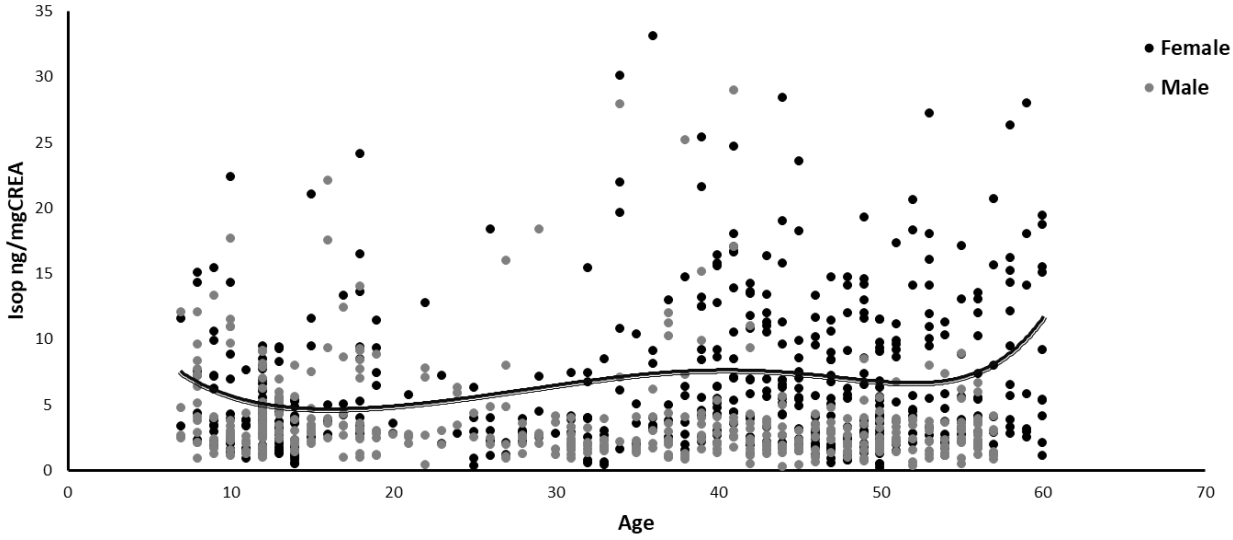

Figure 1. The trend of the 15-F2t-Isop through the lifespan as OS biomarker.

Table 2. Regression model in the whole sample between 15-F2t-Isop (dependent variable) and sex, being OwO, smoking habit and age (continuous) as independent variables.

Regression Model (All Sample)					
F2t-Isop [ng/mg$_{CREA}$]	**B Coef.**	**Std.Err.**	**z**	***p*** **> |z|**	**C.I. [95%]**
Sex	1.2	0.2	6.1	<0.001	0.81/1.6
OwO	−0.3	0.2	−1.4	0.16	−0.7/0.11
Smoke	0.09	0.07	1.3	0.19	−0.05/0.24
Age	0.02	0.005	4.9	<0.001	0.02/0.04

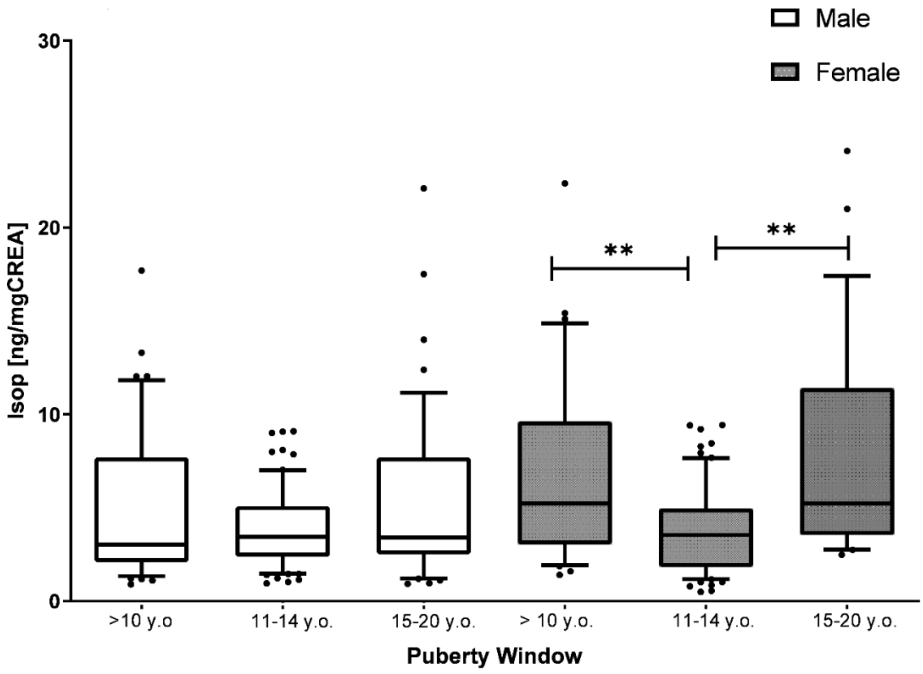

Figure 2. The 15-F2t-Isop levels in the age of puberty (>10 years old = pre-puberty/11–14 years old = puberty/15–20 years old = post-puberty), stratified by sex (** = $p < 0.001$).

Table 3. Pairwise comparisons of means with equal variances in puberty classes (1 = pre-puberty/2 = puberty/3 = post-puberty), stratified by sex.

Pairwise Comparisons of Means with Equal Variances										
	Male					Female				
Puberty Classes	**Tukey Contrast**	**Std.Err.**	**Tukey t**	***p* > |t|**	**C.I. [95%]**	**Tukey Contrast**	**Std.Err.**	**Tukey t**	***p* > |t|**	**C.I. [95%]**
2* vs. *1	−1.8	0.6	−2.8	0.2	−3.4/0.3	−2.8	0.7	−3.9	0.001	−3.1/−0.4
3* vs. *1	0.6	0.8	0.7	0.7	−1.3/2.5	−0.4	0.9	−0.4	0.9	−2.6/1.8
3* vs. *2	2.4	0.7	3.4	0.3	−0.7/4.1	2.4	0.8	2.9	0.01	0.5/4.4

The same pattern of statistical analyses was adopted concerning the menopausal window. In this case too, the regression did not show any significant association in the whole epidemiological sample. Conversely, in the female subgroup, the association between OS and age turned out to be significant [B= −1.01 95% CI −1.5–−0.5, $p < 0.001$]. After the stratification in terms of sex (Figure 3), the pairwise comparisons of means with equal variance (Table 4) showed the same significant V-shape decrease of OS levels in females (Tukey's contrast 4 (pre-menopause) vs. 5 (menopause): −1.5, $p = 0.03$ 95% CI [−3.8/−0.8]; Tukey's contrast 5 (menopause) vs. 6 (post-menopause): 0.4, $p = 0.04$ 95% CI [0.2/2.3]).

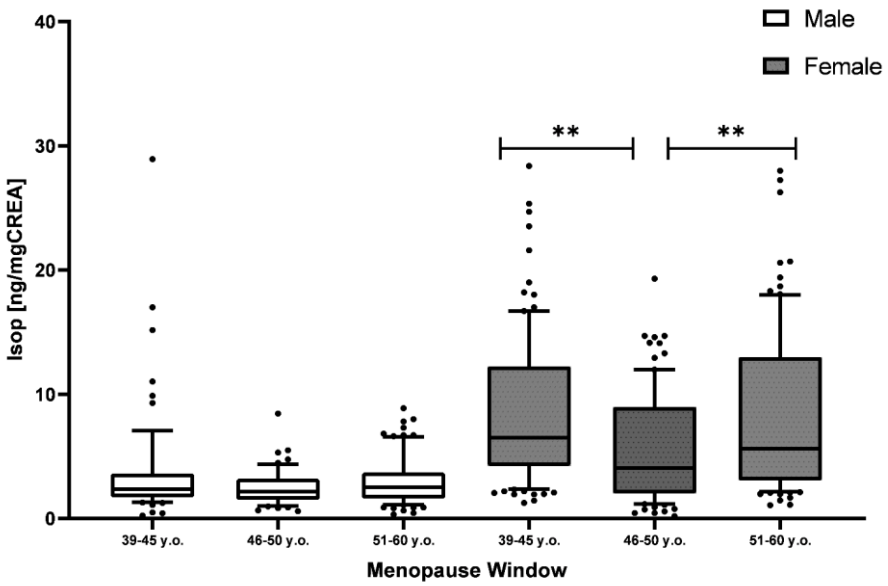

Figure 3. The 15-F2t-Isop levels in the menopause age groups (39–45 years old = pre-menopause/46–50 years old = early menopause/50–60 years old = late menopause), stratified by sex (** = $p < 0.001$).

Table 4. Pairwise comparisons of means with equal variances in menopause classes (4 = pre-menopause/5 = menopause/6 = post-menopause), stratified by sex.

Pairwise Comparisons of Means with Equal Variances										
	Male					Female				
Puberty Classes	**Tukey Contrast**	**Std.Err.**	**Tukey t**	***p* > |t|**	**C.I. [95%]**	**Tukey Contrast**	**Std.Err.**	**Tukey t**	***p* > |t|**	**C.I. [95%]**
5* vs. *4	−1.9	1.1	−1.8	0.17	−4.6/0.6	−1.5	0.9	−1.5	0.03	−3.8/−0.8
6* vs. *4	1.1	1.09	0.9	0.6	−1.5/3.6	−1.1	1.1	−1	0.6	−3.7/1.5
6* vs. *5	3.1	1.1	2.7	0.2	−0.35/5.7	0.4	1.1	0.3	0.04	0.2/2.3

4. Discussion

Our results confirmed an association between OS and aging. The 15-F2t-Isop levels increased with increasing age. However, our research had a cross-sectional design and this

could represent a limitation, as it did not allow the assessment of a causal direction of the observed associations.

However, our results enabled us to lay the groundwork for future analyses. Consistently with previous studies, our findings attested to a direct and positive trend between OS and aging. This process is a time-dynamic mechanism, characterized by the gradual accumulation of damage, progressive functional decline and increased vulnerability to diseases [39]. OS plays a key role in this phenomenon, mainly due to the overproduction of free radicals, such as ROS, overwhelming the body's antioxidant defences [21]. The free radical theory of aging is based on a structural damage-based hypothesis in which age-associated functional losses are due to the accumulation of oxidative injury to macromolecules (lipids, DNA, and proteins) induced by ROS [40]. Nevertheless, the exact mechanism behind this relationship is still not clear, but is probably related to the onset of cellular senescence, a physiological mechanism that stops cellular proliferation in response to damage occurring during replication. In physiological conditions, antioxidants neutralize ROS, preventing the subsequent increase of oxidative damage [1]. However, as the body ages, antioxidant levels and activities decline, leaving the human body susceptible to the onset of several age-related pathologies [39,41].

The most important result of our research was the V-shape OS trend in females in the age windows associated with key hormonal changes: puberty and menopause. In fact, after the stratification by sex, the statistical analyses showed a V-shape association between the 15-F2t-Isop levels and age classes, with a significant decrease in subjects belonging to puberty and early menopause classes. The literature provides some evidence that OS influences the entire reproductive span, even more in women. This OS imbalance, indeed, is frequently combined with a gradual modification in the hormonal profile, particularly in females [42,43]. Recently, many studies have investigated the relationship between hormonal changing and OS during aging and, in particular, during the menopausal window. On the contrary, few researches have investigated the same association in the puberty window [44,45], mainly focusing on pathological conditions (e.g., diabetes and obesity) [46,47] or infertility [48,49]. These studies revealed that the physiologically marked reduction in estrogen during puberty or menopause can result in unbalanced OS in the body, mainly related to the concentration and chemical structure of the estrogen hormone [15]. Specifically, at high concentrations, estrogen tends to have a beneficial antioxidant effect by inhibiting the 8-hydroxylation of guanine DNA bases [21]. On the contrary, low levels of this hormone have pro-oxidant effects, especially when its chemical structure contains a catechol, leading to breaks in genetic material, formation of DNA adducts, and oxidation of bases [50].

Strengths and Limitations

This study has several strengths. First, the use of big data from five different cross-sectional studies, following standardized and homogeneous protocols [25–29], allowed the analysis of a representative sample aged from seven to sixty years of age. Moreover, according to our knowledge, this is the first study investigating the association between hormones and OS simultaneously in puberty and menopausal windows, providing specific data, which matches the important issue of investigating the relationship between hormonal mediations and redox upregulation and balance. In line with previous studies [15,21,22], we provided evidence that hormones, and, in particular, estrogen in females, could mediate and upregulate OS with different results, and this could offer important implications for future research and policies.

The cross-sectional design of the present study and the deficiency of a common protocol represented the main limitations, as these limitations did not allow us to assess the causal direction of the associations, with consequences on the interpretation of the data/results. Another limitation was the lack of precise and hormonally-addressed exclusion/inclusion criteria (e.g., hormonal therapy and contraception, hormonal disorder, premature ovarian failure, and alkaloid therapy), and this must be taken into account for the future analyses.

5. Conclusions

In this perspective, our results supported the fact that hormones, and specifically estrogen, could modulate the 15-F2t-Isop levels, especially during age windows associated with puberty and menopause. Our findings suggested that the V-shape trend in the temporal trajectories of OS may be related to the intrinsic characteristics of estrogen, which is able to modulate and upregulate OS pro- and anti-oxidant mechanisms. A growing number of studies to date have pointed towards the importance of the role of OS in female reproduction, and this evidence must be taken into account. Further investigations are needed to better understand the specific mechanisms through which hormones may interact with oxidative status, to offer valuable knowledge for future studies targeting disease prevention and public health promotion strategies.

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

Data Availability Statement: The data that support the findings of this study are available on request from the corresponding author (G.S.).

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

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