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Prenatal exposure to air pollutants and the second to fourth digit ratio in adult women

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The study aimed to analyse the association between the digit ratio in adult women and the degree of air pollution (suspended particulate matter, sulphur dioxide, nitric dioxide, benzene levels) in the place of residence of their mothers during pregnancy. The data was collected from female students in several Polish cities. Measurements were taken, and questionnaire data were collected. 2D:4D ratios were calculated for the left and the right hand. The ratio was analysed as a continuous variables. Air quality information was retrieved from reports by the Chief Inspectorate for Environmental Protection. Statistically significant differences both in right- and left-hand 2D:4D ratio were found for PM_{10} and benzene. In addition, the right-hand 2D:4D differed significantly depending on $PM_{2.5}$. The association between digit ratio and the complex air pollution index was also found. Poor air quality was associated with higher values of the ratio. Our results indicate that a high airborne pollutant level, especially suspended particulate matter, is associated with a higher digit ratio.

Keywords Air pollution, Digit ratio, In utero exposure, Endocrine disruptors

The second-to-fourth digit ratio (2D:4D) is a commonly used marker in biomedical research. It is subject to strong dimorphic variation, reaching significantly higher values in women than in men[1–3].

Multiple studies have demonstrated a connection between the digit ratio and other sexually dimorphic morphological, physiological and psychological traits, as well as an increased incidence of various diseases. Among other things, the value of this marker is correlated to stature, muscularity and adiposity[4–7], physical ability and fitness[8], respiratory function[9], alcohol, nicotine and game addiction vulnerability[10–13], incidence of aggressive behaviour[14]. With regard to health, a link has been proved between the digit ratio and cancer risk[15,16], cardiovascular diseases[17,18], obesity[19,20], idiopathic pulmonary hypertension[21], congenital adrenal hyperplasia[22], autism spectrum disorders[23], and mental diseases[24]. This list includes only selected traits and conditions related to the ratio. Literature mentions many more traits and diseases: according to the Web of Science database (All Databases), there were 66 studies referring to the digit ratio published in 2023 alone.

The relationship between the digit ratio and other build, personality and health traits is considered to be an effect of exposure to sex hormones in the foetal period. The digit ratio is determined in the early stages of ontogeny, at the end of the third trimester of foetal life, presumably shaped by sex hormones[1]. In this period, exposure to low levels of androgens and high levels of oestrogens is associated with high values of the ratio, whereas high foetal androgen level with low oestrogens is attributed to low values of the ratio. This is due to *Homeobox* and *Hox*genes, which may affect the prenatal production of androgen by controlling the differentiation of the urogenital system as well as digit development[25–27]. The digit ratio is considered a reliable sex hormone level biomarker, and the rationale behind its use has been verified in studies on the correlation between the digit ratio and oestrogen and/or androgen levels in the amniotic fluid, as well as the prevalence of endocrine conditions at later stages of ontogeny[28]. In addition, studies on animal models confirmed that the 2D:4D ratio depends on a balance between testosterone and oestrogen[29,30]. More recently, a handful of studies have negated the relationship between the digit ratio and sex hormones[3,31]. It should be noted, however, that determining foetal hormone levels is an immensely challenging task and one that is frequently impossible both for medical and ethical reasons, mainly due to a high risk of damaging the foetus. Therefore, relevant tests are performed by measuring hormone levels in mothers – which is also beset by technical problems, mostly caused by difficulties

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in recruiting female subjects in the early weeks of pregnancy for research – or in animal models. Such limitations may lead to inconsistent research results.

Biological development and its hormonal regulation in the prenatal period are genetically determined, albeit environmental factors may influence the scope of changes. Certain environmental factors can disturb the endocrine function, affecting foetal development, including digit ratios. There are few studies on the subject and their findings include e.g. the correlation between digit ratio and season of birth, which is explained by daytime duration (light exposure) and melatonin secretion[32], smoking in pregnancy[33]and exposure to bisphenol[34].

Atmospheric air quality is a factor that may impact female health, including endocrine function in pregnancy. Exposure to contaminants increases the risk of premature birth, low weight at birth, and certain genetic disorders[35–38]. Many studies were devoted to long-term consequences of prenatal exposure to air pollution. They are noticeable primarily in respiratory[39]and cardiovascular functions[40]. However, the damaging impact of airborne pollutants is not limited to these two systems. In fact, air pollution has also been proven to affect the nervous and skeletal systems[38]. The effect of air pollutants on the endocrine system is also investigated, as the subject has not been widely discussed. One of the reasons for this scarcity is that the conditions are chronic rather than acute, making it difficult to trace them back to the root cause[41]. The studies published so far merely document the relationship between pollutants, mostly generated by various means of transport, and insulin resistance and type 2 diabetes[42–44], as well as insulin resistance in children[45]. In male adults, elevated exposure to pollutants in place of residence was associated with lower testosterone levels and disruptions in spermatogenesis[46]. The adverse impact of the pollutants is also visible in female reproductive functions. Studies increasingly prove that harmful airborne substances tend to disrupt folliculogenesis and early embryonic growth. This exposure increases the risk of premature birth, low weight at birth, and some genetic disorders[35–38]. Published research findings also indicate the connection between air quality and age at menarche[47].

The authors of the present work did not find any study on the relationship between maternal exposure to ambient air pollution during pregnancy and the digit ratio in their offsprings. This subject has been discussed in this study, the aim of which is to estimate the association between the digit ratio in adult women and the air quality in the place of residence of their mothers during pregnancy.

Materials and methods

The data was collected from 1153 female university students, aged 19–23 y in several Polish cities in the years 2015–2018.

Research was conducted in compliance with all ethical standards prescribed in the Declaration of Helsinki. All experimental protocols were approved by Jagiellonian University's Bioethics Commission (opinion no.122.612047.2016). Informed consent was obtained from all subjects. All participants gave their written consent to take part in the study The procedure involved making anthropometric measurements and gathering survey information. Measurements were taken, and questionnaire data were collected. The research report was described in detail in a previous study[48]. In this study, digits 2 and 4 length values were used. The length of the second and fourth fingers was measured from a midpoint of the flexure-crease proximal to the palm to the tip of the finger in both hands with an accuracy of 0.001 mm, directly by hands using a sliding caliper (Vernier caliper). The measurements were performed by the same person, twice on the left and twice on the right hand, and the average value was taken to minimize the measurements error. The interval between the first and second measurements was approximately 15 min. Next, 2D:4D ratios were calculated for the left and the right hand. The ratio was analysed as a continuous.

Air quality information was retrieved from reports by the Chief Inspectorate for Environmental Protection. It included pollutant levels of particulate matter (PM_{10}, $PM_{2.5}$), sulphur dioxide (SO_2), nitric dioxide (NO_2) and benzene (C_6H_6) over the period of 12 months prior to the month of birth. The data concerned cities without division into boroughs or, for smaller towns, the whole surrounding area (mean value from several measurement stations in the area). Average pollution data for individual months were used and the average value for the 12 months preceding the day of birth of a given person was calculated. Not only the average annual limit was taken into account, but also the number of days in which the daily limit was exceeded. Pollutant level was considered in 3 categories: low, medium, and high. Low category comprised zones where annual pollutant values and the number of days per year with exceedances were below the allowable limit; medium category — zones with annual values below the permissible limit, but with the number of days of exceeding the norm above the limit, and high category included zones above the limit during analysed months. In addition, considering the level of all pollutants, a comprehensive air quality indicator was created. To assess the joint effect of air pollutants, principal component analyses were used to group pollutants (PM_{10}, $PM_{2.5}$, SO_2, NO_2, and C_6H_6) to represent a source-related mixture. The eigenvalue of the factor reached 2.83 and explained 56.4% of common variation in air pollution. The loadings of analysed variables on the air quality index were as follows: PM_{10}–0.54, $PM_{2.5}$–0.51, SO_2 – 0.49, a NO_2– 0.44, benzene – 0.31. Since the first component was relatively high, scores for the single component were used as an indicator of air quality. Tertiles of the component were used to identify three air quality classes: good, moderate, or unhealthy. The detailed criteria were presented elsewhere[47,49] and the supplementary material S1.

The season of birth was considered in four categories: winter (1/12–29/02), spring (1/03–31/05), summer (1/06–31/08), and autumn (1/09–30/11). This division is a good reflection of the seasonal weather variations (temperature, insolation, precipitation) in Poland and corresponds to meteorological seasons of the year in the temperate climate zone. In Poland, the large annual fluctuations of temperature and insolation is typical. Summers are warm, sometimes hot. The average summer temperature is above 15^0C, however, days with temperatures above 30 ^{0}C are very frequent. The average winter temperature is about 0^0C and days with subzero temperatures are very frequent. In spring and autumn, the temperature range between 5 and 15^0C. The warmest month is July, the coolest month is January. The sum of monthly precipitation ranges from 20 to 100 mm/m^2,

Factor	Category	*N*	%
PM_{10}	Low	203	17.61
	Medium	465	40.33
	High	485	42.06
$PM_{2.5}$	Low	238	20.64
	Medium	462	40.07
	High	453	39.29
Benzene	Low	512	44.41
	Medium	290	25.15
	High	351	30.44
SO_2	Low	519	45.01
	Medium	218	18.91
	High	415	35.99
NO_2	Low	370	32.09
	Medium	570	49.44
	High	211	18.30
Season of birth	Winter	271	23.50
	Spring	275	23.85
	Summer	322	27.93
	Autumn	284	24.63
Overall air pollution	Low	322	27.93
	Medium	418	36.25
	High	413	35.82

Table 1. Descriptive characteristics of the subjects.

	Right hand 2D:4D ratio	Left hand 2D:4D ratio
Average	0.9982	0.9993
Median	0.9990	0.9983
Standard deviation	0.0379	0.0392
Minimum	0.8001	0.7998
Maximum	1.2604	1.3450

Table 2. Descriptive statistics.

and it is the highest in the summer months. Days with precipitation ≥ 30 mm occur in Poland only in summer. Average daylight hours per day range from 7 h 48' in December to 16 h 40' in June (Institute of Meteorology and Water Management - National Research Institute IMGW-PIB; http://www.imgw.pl/klimat/). Usually in winters, higher ambient air pollution is recorded, which is due to homes heating and higher car traffic, however, people spent significantly less time outdoor than in summers. Descriptive characteristics of the subjects is presented in the Table 1.

Statistical analysis

To evaluate the differences in the digit ratio depending on the level of air pollution, General Linear Models and two-way analysis of variance were used. Models also included the season of birth. The main effects as well as interactions between factors were tested.

Significance in all statistical tests was set at the level of at least $p < 0.05$.

Results

In the study group the mean age was – 20.6 ± 1.4 SD years, mean body height – 165.3 ± 5.8 SD, and mean BMI – 22.45 ± 3.4 SD. 95 (8.24%) of the surveyed subjects were underweight (BMI < 18.5), while 228 (19.77%) of the surveyed subjects were overweight (BMI ≥ 25). The mean digits 2, digits 4 length values were respectively for right hand: 67.01 ± 3.98, 67.19 ± 4.11, for left hand: 66.85 ± 3.89, 66.97 ± 4.15. Digit ratio values are presented in the Table 2.

Both the right- and the left- hand 2D:4D ratio were not correlated with age (Pearson's correlation coefficient, right hand $r = 0.04$ NS, left hand $r = 0.03$ NS).

Table 3 contains results of statistical analysis using General Linear Models. Statistically significant differences both in right- and left-hand 2D:4D ratio were found for PM_{10} and benzene. In addition, the right-hand 2D:4D differed significantly depending on $PM_{2.5}$. Similar results were obtained when the analysis of the model allowed

	Right hand 2D:4D ratio		Left hand 2D:4D ratio		Right hand 2D:4D ratio		Left hand 2D:4D ratio	
	F	p	F	p	F	p	F	p
PM_{10}	17.85	< 0.001	6.94	< 0.01	17.83	< 0.001	7.12	< 0.01
$PM_{2.5}$	3.24	< 0.05	1.76	NS	3.06	< 0.05	1.71	NS
Benzene	29.83	< 0.001	53.62	< 0.001	29.41	< 0.001	52.14	< 0.001
SO_2	1.22	NS	0.77	NS	1.35	NS	0.67	NS
NO_2	1.70	NS	0.94	NS	1.54	NS	0.88	NS
Season of birth	–	–	–	–	1.20	NS	1.03	NS
Whole model	29.46	< 0.001	26.24	< 0.001	23.20	< 0.001	20.59	< 0.001
R^2	0.23		0.20		0.22		0.20	

Table 3. Results of General Linear models.

Variable	Category	N	Right hand 2D:4D ratio		Left hand 2D:4D ratio	
			mean	SD	mean	SD
PM_{10}	Low	203	0.9691	0.0369	0.9748	0.0376
	Medium	465	0.9966	0.0315	0.9971	0.0398
	High	485	1.0120	0.0340	1.0120	0.0336
$PM_{2.5}$	Low	238	0.9742	0.0380	0.9795	0.0382
	Medium	462	0.9969	0.0342	0.9968	0.0401
	High	453	1.0123	0.0368	1.0126	0.0334
Benzene	Low	512	0.9893	0.0337	0.9891	0.0330
	Medium	290	0.9948	0.0362	0.9920	0.0348
	High	351	1.0142	0.0365	1.0201	0.0426
SO_2	Low	519	0.9925	0.0358	0.9913	0.0368
	Medium	218	0.9984	0.0352	0.9989	0.0372
	High	415	1.9982	0.0378	1.0097	0.0407
NO_2	Low	370	0.9926	0.0364	0.9903	0.0379
	Medium	570	1.0009	0.0376	1.0035	0.0403
	High	211	1.0012	0.0344	1.0049	0.0353
Season of birth	Winter	271	0.9974	0.0353	0.9989	0.0343
	Spring	275	0.9982	0.0346	1.0032	0.0435
	Summer	322	0.9964	0.0414	0.9970	0.0399
	Autumn	284	1.0009	0.0343	0.9993	0.0375

Table 4. Digit ratio in Polish females in relation to air pollutants levels in the birthplace and season of birth.

for the season of birth. All models were found to be statistically significant and accounted for 20–23% overall variability in the digit ratio. The value of 2D:4D increased along with the pollutant level (Table 4).

At the subsequent stage, it was verified whether there were any differences in the 2D:4D ratio depending on air quality in mother's place of residence in the period of 12 months preceding the subject's birth. Air quality was determined by means of a complex index formulated using principal component analysis and taking into account all aforementioned pollutant levels. Results of two-way analysis of variance revealed significant 2D:4D variance between subjects born in areas of different air quality. Poor air quality was associated with higher values of the ratio (Table 5).

The results also show that regardless of the birth season, women whose mothers during pregnancy lived in areas with unhealthy air quality had the higher values of digit ratios than women whose mothers during pregnancy lived in areas with good air quality (Figs. 1 and 2).

Discussion

Our results imply a significant relationship between a complex air quality index and digit ratios. The model which comprised all analysed pollutants accounts for as much as 20%-digit ratio variability. Exposure to high air pollutants levels in the foetal period is associated with elevated 2D:4D values. The effect is more marked for the right hand, a finding in line with other studies. Right-hand 2D:4D is considered more sensitive to sex hormones than the left-hand digit ratio[50].

A higher digit ratio in women whose mothers lived in areas of poor air quality is presumably due to the fact that certain air pollutants may disrupt endocrine function.

	Right hand 2D:4D ratio			Left hand 2D:4D ratio		
Air quality	***N***	**Mean**	**Sd**	***N***	**Mean**	**sd**
Good	322	0.9904	0.0353	322	0.9896	0.0349
Moderate	418	0.9972	0.0362	418	1.0009	0.0366
Unhealthy	413	1.0054	0.0358	413	1.0056	0.0357
The results of ANOVA						
Factor: air quality			F = 15.40 $p < 0.001$		F = 14.82 $p < 0.001$	
Factor: season of birth			F = 1.00 NS		F = 1.05 NS	
Factors: air quality & season of birth			F = 2.00 NS		F = 0.89 NS	

Table 5. Digit ratio in Polish females in relation to air quality in the birthplace.

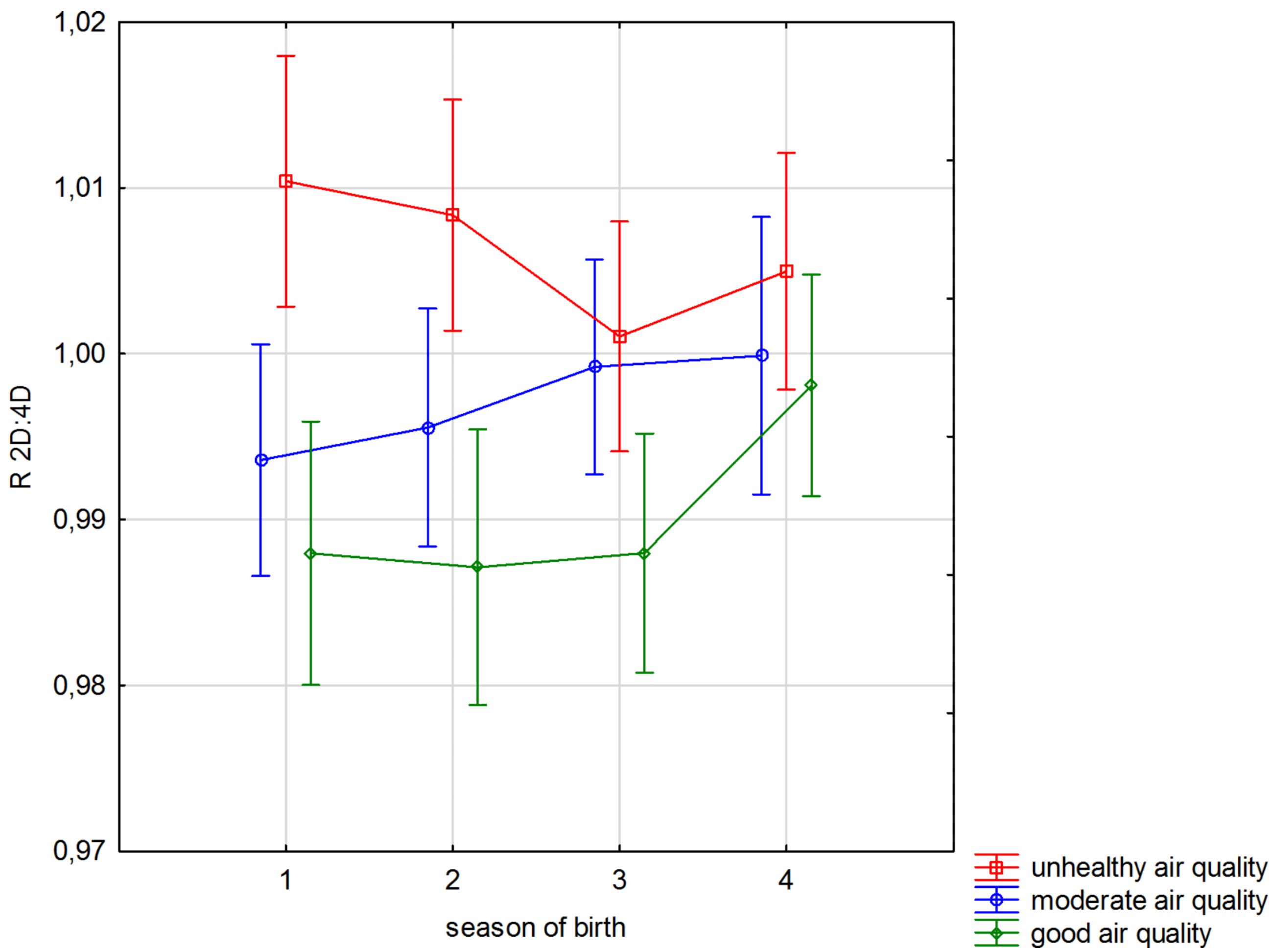

Fig. 1. The values of right hand digit ratio by season of birth and air quality in the birthplace. Season of birth: 1- winter, 2- spring, 3- summer, 4- autumn.

Many substances present in human environment are regarded as endocrine disruptors, which interact with the human endocrine system and affect its function. This leads to endocrine-related diseases and disorders in the biological development of children[51]. Endocrine-disrupting chemicals (EDCs) interact with various hormones and consequently affect the functions of various organs and systems. EDCs can also inhibit the synthesis of sex steroids or interfere with their metabolism. Children and adolescents are particularly vulnerable to the negative effects of endocrine disruptors. Studies increasingly emphasize the long-term consequences of EDC exposure in the foetal period, although their findings are inconsistent.

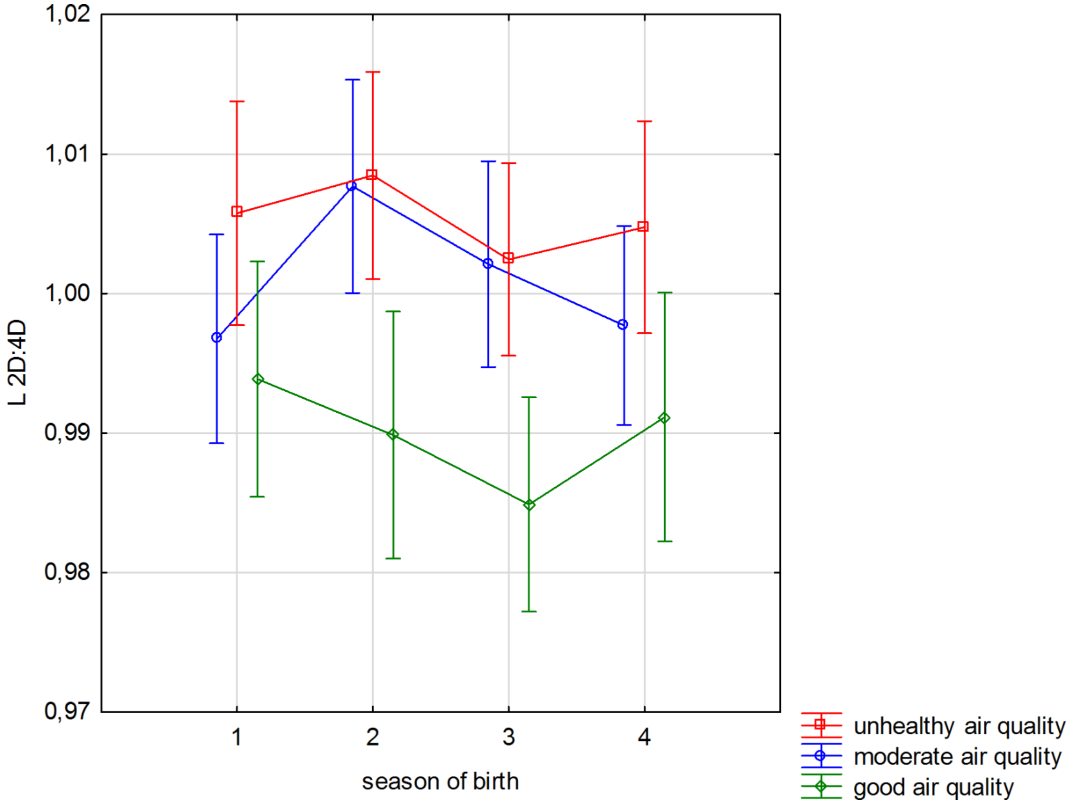

Fig. 2. The values of left hand digit ratio by season of birth and air quality in the birthplace. Season of birth: 1- winter, 2- spring, 3- summer, 4- autumn.

Most studies on this subject discuss the impact of bisphenol A, phthalates, ethane, DDT and parabens[52]. The category of endocrine disruptors also includes atmospheric air pollutants, mainly substances present in suspended particulate matter: heavy metal (lead, cadmium), dioxins, and PAHs. The studies referred to in the introduction demonstrate the severity of the impact of these substances on human health and biological development at various stages of ontogeny. The respiratory system is not the only route through which airborne substances enter the body. In fact, they contaminate water, plants and animals later become human food. Effects of delayed exposure are hard to estimate. Human development is extremely long, and it is difficult to obtain data on both: exposure to harmful substances in the early stages of development and biological condition in adulthood. Determining exposure levels is also a complex task. One solution is to measure the level of harmful substances in blood or other bodily fluids, bearing in mind that their concentration may vary over time. If exposure during the prenatal period is to be determined, the most common method involves taking cord blood or measuring the content of specific substances, e.g. heavy metals, in the placenta; nevertheless, exposure to harmful substances may have been entirely different at the beginning and at the end of pregnancy. These methodological issues may have led to inconsistencies in results reported by various authors.

As mentioned before, very few studies to date have been published on the connection between exposure to endocrine disruptors in the foetal period and the digit ratio. Two studies analysed the effect of prenatal exposure to EDCs such as 2,3,7,8-tetrachlorodibenzo (TCDD) and polybrominated biphenyl-153 (PBB-153) on digit ratio[53,54]. The former study did not reveal any relationship between in utero exposure to TCDD and altered 2D:4D ratio. Likewise, no significant connection was reported by Wainstock et al[54]. However, in the female group, prenatal exposure to high PBB levels led to a slightly higher digit ratio. It is worth noting that the test group was very small and comprised of merely 19 males and 32 females. Also, Chen et al[55].. investigated the effect of prenatal exposure to polybrominated diphenyl ethers (PBDEs) on the second to fourth digit ratio in children aged 4 years from the Shanghai-Minhang Birth Cohort Study. Cord blood samples at delivery were collected and nine PBDE congeners were measured. Results show that exposure to PBDE in the prenatal period leads to an elevated digit ratio both in boys and girls. Other research discussed the impact of bisphenol A (BPA). Studies on animal models (rats) demonstrate that prenatal exposure to BPA is associated with an increased value of the ratio in males[29]. On the other hand, studies conducted on humans by Arbuckle et al[56].. did not reveal any connection between exposure to BPA and digit ratio in boys, but they did show an inverse correlation between exposure to BPA and the digit ratio. Other studies proved that smoking tobacco during pregnancy increased the digit ratio in children[5].

To the best of our knowledge, this study is the first one to analyse the relationship between air pollution and the digit ratio. Our results show that a high airborne pollutant level, especially suspended particulate matter, is associated with a higher digit ratio. As this study was based only on data from female subjects, it might be necessary to run similar tests among male subjects to verify whether air pollutants also 'feminize' digit ratios in men.

The present research has certain limitations, related primarily to the determination of exposure to harmful substances in the atmospheric air during pregnancy. Although the Digit Ratio is formed in the early stages of prenatal development, we included pollution data from the period including 12 months before birth. This was largely due to the fact that the standards for determining the degree of air pollution were developed for such a period, and thus it was possible to divide this variable into categories. Due to changes in the level of contamination during the year, the analysis included the birth season, but in our group, it did not have a significant impact on the DR value. Available data concerned air pollution in mother's place of residence in pregnancy. It should be noted, however, that significant differences in air quality may occur even in the same region, which may be caused by e.g. wind direction, proximity to public roads or green areas. An individual's exposure is also related to their activity, travelling within the area and the time spent indoors or outdoors. In addition, the composition of suspended particulate matter, which proved to have the greatest impact on the digit ratio, can also differ by region. Obviously, we are in no position to claim that the exposure levels were accurately determined. Still, it is practically impossible to establish them with precision. The second limitation is the lack of data on other adverse factors that could affect the digit ratio, e.g. the mother's smoking, her exposure to harmful chemicals in the workplace. An advantage of our research is that it involved a large number of subjects all over the country, coming from areas differing in terms of air quality.

Conclusions

Associations between both right- and left-hand 2D:4D ratio in adult women and the degree of air pollutants: PM_{10} and benzene in the place of residence of their mothers during pregnancy were found. In addition, the right-hand 2D:4D differed significantly depending on $PM_{2.5}$. The value of 2D:4D rose along with pollutant level. A similar trend was observed in an analysis of the association between digit ratio and the complex air pollution index. Poor air quality was associated with higher values of the ratio.

Our results indicate that air pollutants disrupt the correct function of the endocrine system as early as during foetal development. The impact of these disruptions may be manifested both in the prenatal period and at a later stage, particularly if the child continues to be exposed to high pollutant levels.

Data availability

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to containing information that could compromise the privacy of research participants.

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Conceptualization and Methodology- I.W.; Data Collecting- K.K. and I.W; Statistical Analysis - W.F. and P.P.; Original Draft Preparation – W.F. and I.W.; Review and Editing - P.P and A.S.; Supervision - I.W. and A.S.

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Declarations

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