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The effectiveness of an intervention to reduce exposure to trace metals during or prior to pregnancy: A prospective study in urban and rural locations

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A R T I C L E I N F O

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A B S T R A C T

Background: Prenatal exposure to trace metals can have adverse effects on health and increase the risk of developing certain diseases. This study aimed to determine the effectiveness of giving women advice to reduce their exposure to trace metals during pregnancy or prior to conception. The study also examined differences in exposure between rural and urban environments in southern France.
Methods: In this prospective study, pregnant women or those intending to conceive were recruited from two medical centers for gynecology/obstetrics (rural location: Saint-Rémy-de-Provence; urban location: Marseille). Hair samples were collected and analyzed to determine the levels of exposure to trace metals. Participants with 'risky' levels were given corresponding advice sheets on how to reduce their exposure or, for certain metals, they were encouraged to find out about potential sources of exposure. A second hair sample was collected and analyzed 3 months later.
Results: It was found that 109 women had 'risky' levels of exposure to trace metals, out of a total of 184 women (59.2 %). Cerium was the most frequently identified metal ($N = 26$), followed by nickel ($N = 23$), and titanium ($N = 19$). There were more women at the urban center with 'risky' levels (56/86; 65.1 %) than at the rural center (53/98; 54.1 %), but this difference was not statistically significant ($p = 0.13$). Advice sheets were given to 64 of the 109 participants with 'risky' levels (58.7 %), but only 21 returned for the second hair analysis. Of these, 14 were found to have reduced their exposure, which corresponds to just 12.8 % (14/109) of the participants with 'risky' levels.
Conclusions: These results indicate that it would be helpful to develop new interventions to reduce trace metal exposure during or prior to pregnancy.

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1. Introduction

Chronic exposure to environmental pollutants can lead to diseases including cancer, cardiovascular diseases, and respiratory disorders [1,2]. Particularly harmful pollutants include trace metals, such as lead and mercury, which are well-known to be toxic [3,4]. These metals can be found in the air [5], food, and water [4], as well as in cosmetics [6,7], cigarettes [8–10], industrial sites [11], and tattoos [12]. Although standards have been developed to ensure safe levels of exposure to trace metals, most notably in drinking water and food, it is sometimes found that the levels exceed the recommended limits [13,14].

Some trace metals are known to be particularly toxic, such as arsenic and cadmium [15–17], while others are essential for normal physiological functioning, such as copper and iron. However, at high concentrations even the essential trace metals can become harmful and may lead to organ damage and cancer [18,19]. It is thought that similar mechanisms may underlie the harmful effects of different trace metals. Specifically, there is evidence that exposure leads to an increase in reactive oxygen species, which then results in oxidative stress and cellular damage [14]. This in turn can cause various diseases [20].

Exposure to harmful levels of trace metals is particularly problematic during pregnancy, as it affects the fetus at a critical stage of early development. This is thought to have a detrimental effect on health over the long term, increasing the risk of developing various diseases later in life [21]. For instance, prenatal exposure to cadmium has been linked to the later development of asthma, eczema, and food allergies [22], and prenatal exposure to arsenic has been associated with childhood allergic rhinitis [23] and an increased risk of acute myocardial infarction and cancer [24]. There is also evidence that *in utero* exposure to lead is negatively associated with neuropsychological performance during childhood [25], and exposure to certain metals, such as cadmium and mercury, has been linked to preterm birth [26], neural tube defects [27], and congenital heart defects [28].

It has been reported that women contemplating pregnancy increasingly express concern over the effects of environmental pollutants [29]. However, clinicians often find it challenging to address these issues, particularly because the levels of exposure may not be known [30]. One approach that can be adopted is to obtain measures of exposure in clinical practice, such as urine analyses, blood tests, or hair analyses. The latter may be particularly convenient for clinical use as collecting hair samples is rapid, non-invasive, and well-tolerated, and the hair samples provide a measure of exposure over the last days or months, with 1 cm of hair representing around one month of growth. As environmental substances accumulate in the hair protein filament as it grows, it is therefore possible to trace the levels of exposure over time [31,32] and to identify any that are potentially dangerous.

Another difficulty faced by clinicians is lacking the training and tools to deal with the issue of environmental pollutants [33]. However, this could be addressed by adopting interventions that help patients to reduce their exposure. For instance, one simple approach would be to use pre-prepared advice sheets that could be given to patients according to their levels of exposure. For instance, if high levels of mercury are identified, patients could be given advice to reduce their consumption of large fish (e.g., tuna), a well-known source of exposure to mercury [34]. However, to the best of our knowledge, there are no studies assessing the effectiveness of such advice sheets for reducing harmful levels of exposure. This therefore represents a gap in the literature that we sought to address. If the approach can be shown to be effective, it would strongly support its adoption in clinical practice and have potential implications for public health strategies.

In this study, we examined whether a simple intervention, namely advice sheets, could be used to protect children from harmful trace metals prior to birth. For this, we assessed women's levels of exposure to trace metals using hair sample analyses, and we examined whether advice sheets could help the women to reduce any 'risky' levels over a period of three months. We focused exclusively on pregnant women and those intending to conceive because of the importance of reducing harmful exposure during prenatal development. We also reasoned that the women would be highly motivated to follow the advice. We carried out the study at two different medical centers for gynecology/obstetrics to compare the levels of exposure for urban and rural regions, as differences have been found in in previous studies [35–37]. Both medical centers were in France, where women can see a gynecologist of their choosing without a referral from their general practitioner (GP), and where medical consultations take place prior to conception and then every month during pregnancy (from the third month).

Our main hypothesis was that pregnant women, or those intending to conceive, would successfully reduce their exposure to trace metals by following advice provided on information sheets. We also hypothesized that women attending an urban medical center would have more trace metals at 'risky' levels than those attending a rural center.

2. Material and methods

2.1. Study design

This study was a prospective, multicenter, open-label cohort study. It was approved by the Committee for the Protection of Persons and was conducted in accordance with the principles of good clinical practice, the Declaration of Helsinki, and French law (number 2004-806). The study was registered on clinicaltrials.gov (identifier: NCT05144438).

2.2. Setting

The study was carried out at two medical centers for gynecology/obstetrics: one in an urban location and the other in a rural location. The urban location was the city of Marseille, France, which has approximately 880,000 inhabitants; the rural location was the town of Saint-Rémy-de-Provence, France, which has approximately 9800 inhabitants and is around 90 km from Marseille. Participants were recruited over a period of 3 months (from April 1, 2021, to June 30, 2021), and for each participant, the study lasted for 4 months.

2.3. Participants and procedure

We recruited participants who met the inclusion criteria: female (sex assigned at birth), aged 18 years or older, affiliated to the French social security system, and either intending to conceive or in the first trimester of pregnancy. Participants were excluded who were under guardianship or did not provide informed consent to participate in the study.

The recruitment took place during appointments for preconceptual care or early pregnancy (from April 1, 2021, to June 30, 2021). This was carried out by two doctors at the rural center and one doctor at the urban center. All women who fulfilled the inclusion criteria were informed about the study and were offered a hair sample analysis at the end of their appointment to assess their levels of exposure to trace metals (visit 1). These tests were chosen because they are rapid and well-tolerated, and they provide a measure of exposure over the last few months. The women were invited to return one month later to receive the results of the hair analysis (visit 2). For each trace metal, the levels were shown to be 'not risky' or 'risky.' Women who were found to have 'risky' levels for at least one trace metal were given the corresponding advice sheets on how to reduce their exposure (at visit 2). These were available for aluminum, antimony, cadmium, lead, mercury, tellurium, thallium, tin, and titanium. They were then invited to return after three months (visit 3). A second hair sample was taken at the final visit (visit 3) to determine whether the 'risky' levels of exposure had been successfully reduced (see Fig. 1). The women were not paid for taking part in the study.

2.4. Advice

The advice sheets were developed by Toxseek (Ennery, France) and are based on previous research (e.g., Sundar and Chakravarty, 2010) [38,39]. They explain the dangers of exposure to trace metals and how to avoid them. The participants were only given advice sheets that corresponded to metals found to be at 'risky' levels. They were asked to follow the advice for three months, and they were given the opportunity to ask questions. The clinicians checked that the participants understood the advice.

The specific advice varied according to the trace metal (see Table 1). For example, for 'risky' levels of mercury, participants were advised to eat fish no more than twice a week, to avoid eating large fish (e.g., tuna), and to have dental amalgam fillings replaced. For titanium, participants were advised to avoid products containing titanium dioxide (E171) and to choose organic sunscreens that do not contain chemical filters or nanoparticles. For antimony, participants were advised to drink tap water rather than bottled water, to regularly aerate their homes, and to wear protective clothing/equipment if they were exposed to the metal at work. For tellurium, participants were given a list of potential sources of exposure and asked to identify those that might be the cause. If 'risky' levels were found for trace metals that did not have a corresponding advice sheet, the clinicians were able to provide advice verbally, and the participants were encouraged to find out about possible sources of exposure themselves (e.g., on the Toxseek website and other websites) and to think about how their lifestyles could affect their exposure levels.

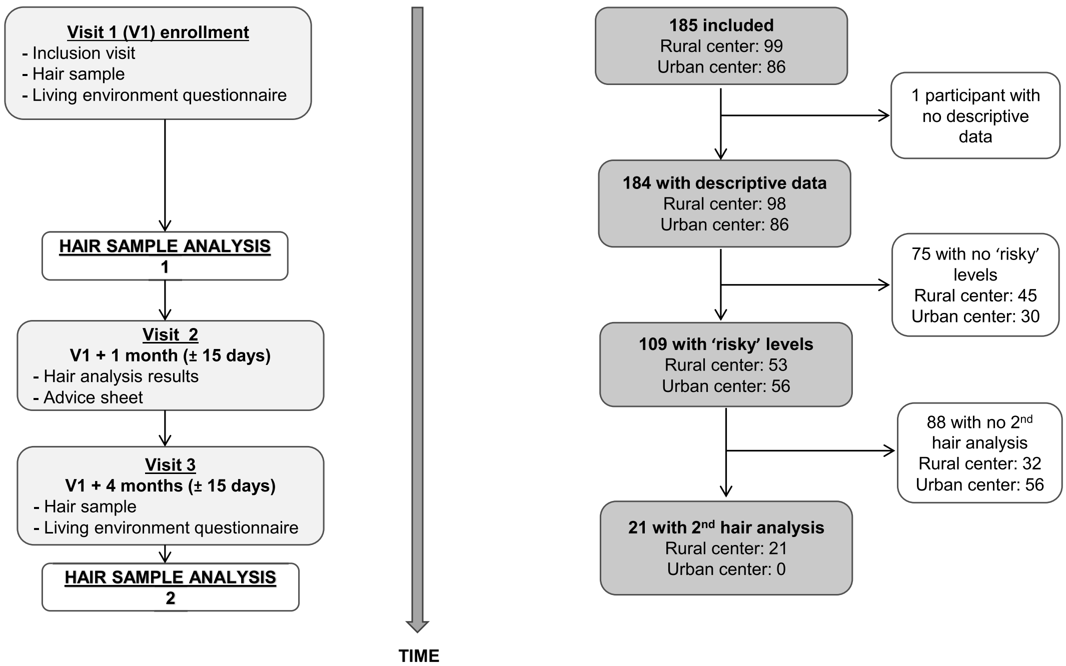

Fig. 1. Study timeline and the number of participants
The rural medical center is in Saint-Rémy-de-Provence; the urban medical center is in the city of Marseille.

Table 1
Information from the advice sheets: potential sources of exposure to trace metals and advice on reducing exposure.

METAL	Potential sources of exposure:	Advice
Aluminum	Naturally present at low levels in food, with higher levels (5–10 mg/kg) found in bread, cakes, certain vegetables, and dairy products, and even more in spices, cocoa, and tea. Present in several food additives: E173, E520-E523, E541, E554-E556, and E559. In total, 95 % of our aluminum intake comes from food; part of the remaining 5 % comes from tap water (naturally present or from aluminum sulphate and aluminum chloride used for treating water). Kitchen utensils made from aluminum may contaminate acidic foods. Aluminum is used for food packaging (e.g., soft drinks cans, Tetra Pak cartons, 'tin' cans) and cooking, which may contaminate food/drinks if they are acidic or heated. Aluminum can be found in cosmetics and medication, and it used in industry.	- Avoid cooking utensils made from aluminum or change them as soon as they are damaged. - Whenever possible opt for glass jars when storing food, especially baby milk. - Check the best before date on drinks cans because the longer the liquid has been in the can the greater the risk of contamination. - Check the level of aluminum in your tap water on the website solidarites-sante.gouv.fr. This should not exceed 0.2 mg/l. - Use greaseproof paper instead of aluminum foil for cooking food and avoid contact between the foil and acidic foods. - Choose organic food and avoid products containing E173, E520-E523, E541, E554-E556, and E559. - Don't use anti-perspirants that contain aluminum salts. - Avoid antacids or only use them very occasionally.
Antimony	High levels sometimes found in mineral water (from PET plastic bottles). Metal and chemical industries (present in alloys for lead-acid battery plates, solder alloys, ammunition, metal coating, semiconductor materials, flame retardants, PET plastic, some glass and earthenware, some pigments), mines, and fireworks.	- Drink tap water rather than bottled water. Use a glass or stainless-steel water bottle when traveling. - Regularly aerate your home (for 10 min twice a day). - For occupational exposure, use personal protective equipment.
Cadmium	Exposure to cadmium from agriculture (e.g., phosphate fertilizer), the metal industries, cigarette smoke, food (lettuce, cabbage, spinach, grains, mushrooms, rice, oysters), and air pollution (burning household waste, coal, and oil; steel industry; batteries).	- Stop smoking. - Choose organic food. - For occupational exposure, use personal protective equipment.
Lead	Metal industries, industrial waste, certain paints, old pipes, certain cosmetics.	- If your home was built before 1948, check whether the paint contains lead. If so, it should be stripped and repainted by a professional. - Check the level of lead in your tap water. - For occupational exposure, use personal protective equipment. - Wash your hands after touching objects made of lead.
Mercury	Present in certain foods, particularly predatory fish (tuna, swordfish, bass, shark, marlin, grenadiers, bream), and shellfish (oysters, mussels). Present in dental amalgam, industrial waste (e.g., gold mining, metal industries), fossil fuel emissions, oil refineries, incinerators, recycling industry, volcanic emissions, and some geysers.	- Avoid eating large fish too often (tuna, salmon, swordfish, bream, shark, bass, marlin, grenadiers). Eat fish no more than twice a week and choose small fish. - Get any amalgam fillings replaced by your dentist.
Tellurium	Used in certain infra-red devices, rubber, ceramic pigments, biocides, catalysts, synthetic organic chemistry.	- Identify the source of contamination from the list.
Thallium	Used in thermometers for very cold regions, infra-red detectors, lighting (green light), myocardial perfusion scans with Tl-201, television cameras, certain insecticides, and rat poison.	- Avoid contact with rat poison. - Identify the source of contamination from the list.
Tin	Used for storing food (tin foil) and for tubes of toothpaste or paint (although aluminum is more common). It can be present in tableware and decorative objects, certain toys (e.g., tin soldiers), taps, welds, coins, musical instruments (bells, cymbals, organ pipes), and metallic coating.	- Wash your hands after touching anything made from tin. - If using a paint that contains tin (triethyltin), wear a mask and work in a well-ventilated area.
Titanium	Present as titanium dioxide (E171) in confectionary (candy, chewing gum), medicines, and cosmetic products, including two-thirds of all toothpastes.	- Avoid foods and cosmetics that contain titanium dioxide (E171). - Use organic sunscreens that do not contain chemical filters or nanoparticles.

2.5. Outcome measures

Primary outcome measure: The proportion of participants who successfully reduced their exposure to trace metals. Success was inferred if the number of 'risky' trace metals in the final hair sample was lower than in the initial hair sample.

Secondary measure of interest: Differences in the number of participants with 'risky' levels of exposure to trace metals at the rural and urban medical centers.

2.6. Data collection

Hair Samples. These were taken at visits 1 and 4. The samples were collected by following the guidelines provided by the Toxseek (Ennery, France). The samples were around 3 mm in diameter (approximately 50–70 hairs), cut at the scalp, and trimmed to 3 cm from the base. They were placed in a collection tube (labelled with a barcode) and sent by post to Toxseek, which carried out the toxicological analyses. The company's procedures include washing the hair samples to avoid interference from potential contaminants (e.g., dust, hair products), and analysis using inductively coupled plasma mass spectrometry [40]. The results show the levels of 49 different metals and highlight those that are 'risky.' The levels defined as 'risky' are shown in Table 2; these were determined by Toxseek and are based on previous studies (e.g., Goullé et al., 2010) [41–43].

Adherence questionnaire. The participants' adherence to the advice was assessed using a questionnaire, which was sent to them by email. The questionnaire asked participants to report whether they had been able to follow the advice and the reasons for any

Table 2
List of trace metal levels considered 'risky'.

Metal	'Risky' level
Aluminum	>25.6 µg/g
Antimony	>0.1 µg/g
Arsenic	>0.3 µg/g
Barium	>4.0 µg/g
Beryllium	>0.01 µg/g
Boron	>2.5 µg/g
Cadmium	>0.4 µg/g
Cerium	>0.01 µg/g
Cesium	>0.001 µg/g
Chromium	>11.0 µg/g
Cobalt	>2.9 µg/g
Copper	>35.0 µg/g
Dysprosium	>0.003 µg/g
Erbium	>0.003 µg/g
Europium	>0.001 µg/g
Gadolinium	>0.005 µg/g
Gallium	>0.012 µg/g
Hafnium	>0.05 µg/g
Holmium	>0.001 µg/g
Iron	>44.0 µg/g
Lanthanum	>0.02 µg/g
Lead	>1.0 µg/g
Manganese	>2.41 µg/g
Mercury	>1.7 µg/g
Molybdenum	>3.4 µg/g
Neodymium	>0.01 µg/g
Nickel	>1.6 µg/g
Niobium	>0.005 µg/g
Praseodymium	>0.001 µg/g
Samarium	>0.003 µg/g
Selenium	>2.0 µg/g
Silver	>0.5 µg/g
Strontium	>6.0 µg/g
Tantalum	>0.001 µg/g
Tellurium	>0.003 µg/g
Thallium	>0.0016 µg/g
Thorium	>0.01 µg/g
Thulium	>0.001 µg/g
Tin	>1.4 µg/g
Titanium	>5.0 µg/g
Tungsten	>0.1 µg/g
Uranium	>0.436 µg/g
Vanadium	>2.8 µg/g
Ytterbium	>0.005 µg/g
Zinc	>300.0 µg/g
Zirconium	>0.7 µg/g

problems. They were also asked how difficult it had been to follow the advice and whether it required much effort.

Living environment questionnaire. Participants were given this questionnaire at visits 1 and 4. It included items about accommodation, the surrounding environment, drinking water, organic food, and the work environment. The full questionnaire is shown in the supplementary material (Supplementary Material 1).

2.7. Sample size

We carried out a pilot study on 45 women at the Saint-Rémy-de-Provence medical center for gynecology/obstetrics. All of the women were in their first trimester of pregnancy. We found that 17 of the women (38 %; 95 % confidence intervals [25.1, 52.4]) had 'risky' levels of exposure to at least one trace metal. On this basis, we estimated that around 200 women would be needed to obtain 50 participants with 'risky' levels of exposure (lower limit of the confidence interval). This latter number is important, as the success of the intervention is determined based on these participants alone.

Based on data from our pilot study, we estimated that 30 % of the participants with 'risky' levels of exposure would have reduced levels for the second hair analysis in the absence of advice, and that this proportion would rise to 50 % when given advice to follow. We calculated that with 50 participants, it would be possible to detect this 20 % difference (two-tailed Z-test) with a power of at least 80 % and an alpha level of 5 %.

2.8. Statistical analyses

For the primary outcome measure, the statistical analysis included the women who were initially found to have 'risky' levels of exposure to trace metals. The proportion of these women who successfully reduced their exposure was calculated (i.e., those with fewer metals at 'risky' levels in the second hair sample), along with the 95 % confidence intervals, as determined using Wilson's method. This proportion was compared to a 30 % reduction without advice using a chi-square test. A significantly higher proportion was taken to indicate that the intervention successfully reduced the participants' exposure to trace metals.

The proportion of women with 'risky' levels of exposure was determined for the rural and urban medical centers. The difference was analyzed using a chi-square test. Further differences between participants at the rural and urban medical centers were analyzed using t-tests for the normally distributed data, Wilcoxon tests for the non-normally distributed data, and chi-square or Fisher's exact tests for the categorical data.

Univariate logistic regression analyses were run to identify potential risk factors for 'risky' levels of exposure to trace metals, using data from all study participants at the inclusion visit. All variables with $p < 0.2$ were selected and included in a multivariate logistic regression analysis. Any variables found to have $p < 0.05$ were concluded to be risk factors for 'risky' levels of exposure to trace metals.

3. Results

3.1. Study participants

A total of 185 women were recruited for the study: 99 (53.5 %) at the rural medical center and 86 (46.5 %) at the urban center (see Fig. 1). One participant was excluded as no descriptive data were available. The women were 19–47 years old (mean: 32.4 ± 5.4) and 109 (59.9 %) were pregnant (see Table 3); the 76 other women all intended to conceive. There were 25 participants (14 %) who took vitamin supplements, 25.8 % were smokers, and 34.8 % had a tattoo.

3.2. Participants with 'risky' levels of exposure to trace metals

A total of 109 participants (59.2 %) were found to have 'risky' levels of exposure to at least one trace metal. Of these, 56 (51.4 %) had 'risky' levels for just one metal and 35 (32.1 %) had 'risky' levels for two metals (see Fig. 2). We counted how many times each different metal was found to be 'risky' in the initial hair analyses and found that the rare-earth element cerium (N = 26; 23.9 %) had the highest frequency, followed by nickel (N = 23; 21.1 %), titanium (N = 19; 17.4 %), iron (N = 15; 13.8 %), and tellurium (N = 13; 11.0 %; see Table 4 for all metals identified). Metals that are well known to be toxic, even at low levels, were also identified, including mercury (N = 4; 3.7 %) and lead (N = 1; 0.9 %).

3.3. Primary outcome: participants who successfully reduced their 'risky' levels of exposure

Of the 109 participants with 'risky' levels of exposure to trace metals, 64 received advice sheets on how to reduce their exposure (visit 2). The participants were then invited to return for a second hair analysis 3 months later (visit 3). However, only 21 participants

Table 3
Demographic and clinical characteristics of the study participants at the inclusion visit.

	Rural Center (N = 98)	Urban Center (N = 86)	Total (N = 184)	Difference
Mean age ± standard deviation, years	31.9 ± 5.4	33.0 ± 5.3	32.4 ± 5.4	P < 0.0001[a]
Median weight (IQR), kg	61 [44–55]	60 [44–54]	60 [44–55]	P < 0.0001[b]
Pregnant, N/total N[a]	76/96 (79.2 %)	33/86 (38.4 %)	109/182 (59.9 %)	P < 0.0001[c]
Employed, N/total N[a]	83/89 (93.3)	77/84 (91.7)	160/173 (92.5)	P = 0.69[c]
Diabetic, N	2	1	3	
Food allergy, N	1	5	6	
Taking medication, N/total N[a]	16/97 (16.5 %)	9/86 (10.5 %)	25/183 (13.7 %)	P = 0.24[c]
Taking vitamin supplement, N/total N[a]	0/94 (0 %)	25/85 (29.4 %)	25/179 (14 %)	P < 0.0001[d]
Smoker, N/total N[a]	21/96 (21.9 %)	26/86 (30.2 %)	47/182 (25.8 %)	P = 0.2[c]
Median number of e-cigarettes per day (IQR)	5 [2–10] N = 19	8 [2–10] N = 24	5 [2–10] N = 43	P < 0.0001[b]
Metallic orthodontic appliance, N/total N[a]	2/96 (2.1 %)	1/86 (1.2 %)	3/182 (1.6 %)	P = 1[d]
Tattoo, N/total N[a]	7/55 (12.7 %)	42/86 (48.8 %)	49/141 (34.8 %)	P < 0.0001[c]
Median tattoo surface area (IQR), cm^2	5 [4–14] N = 7	3 [2–19] N = 42	4 [2–15] N = 49	P = 0.11[b]

Statistical tests: a: *t*-test; b: Wilcoxon test; c: chi-square test; d: Fisher's exact test.
Abbreviation: IQR: inter-quartile range.
[a] The total N indicates the data that were available.

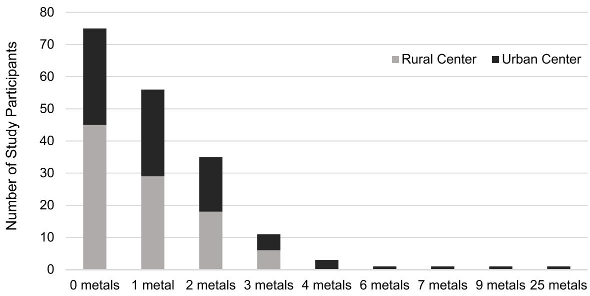

Fig. 2. Number of trace metals at 'risky' levels at visit 1.

Table 4
Number of times each trace metal was found to be at 'risky' levels in the initial hair samples.

Trace metal	Rural Center	Urban Center	Total
Cerium	11	15	26
Nickel	9	14	23
Titanium	11	8	19
Iron	7	8	15
Tellurium	10	2	13
Silver	3	7	10
Strontium	3	6	9
Lanthanum	3	5	8
Other rare-earth elements	3	4	7
Antimony	2	4	6
Gadolinium	2	4	6
Manganese	1	5	6
Aluminum	2	3	5
Europium	3	1	4
Mercury	2	2	4
Tin	1	2	3
Tantalum	0	3	3
Barium	1	1	2
Chromium	1	1	2
Neodymium	1	1	2
Niobium	2	0	2
Thulium	1	1	2
Copper	0	1	1
Gallium	1	0	1
Lead	0	1	1
Zirconium	0	1	1

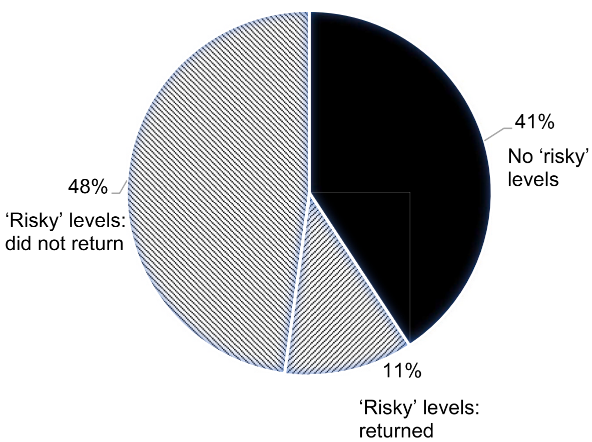

Fig. 3. Proportion of study participants with 'risky' levels of a trace metal
The chart shows the proportion of participants with 'risky' levels who returned or did not return for a second hair sample analysis.

returned for this final visit (see Fig. 3), and this was around 5–6 months after the initial hair analysis. Of these, it was found that two-thirds had successfully reduced their exposure (14/21; 66.7 %; 95 % confidence intervals [45.4, 82.8]), including 10 participants who no longer had any 'risky' levels for any trace metal (Table 5). The metals that were found to have reduced levels (no longer 'risky') included cerium (two subjects), the other rare-earth elements (three subjects), tellurium (five subjects), and nickel (four subjects; see Table 6 for full list).

A statistical analysis was run, which included participants with 'risky' levels of exposure who did not return for the final test; these participants were considered by default to have failed to reduce their exposure to the trace metals. This gave a total success rate of 12.8 % (14/109; see Fig. 4). A chi-square test showed that this percentage was significantly lower than the 30 % expected in the absence of advice ($\chi^2 = 15.3$; $p < 0.0001$).

As this low success rate could at least partly relate to difficulty avoiding exposure and failing to persevere, we examined whether the participants reported finding it easy or difficult to avoid exposure to the trace metals. We found that eight of the 19 respondents (42.1 %) reported that they found it difficult. We also examined whether the participants reported that it required effort to avoid exposure; of the 26 respondents, 23 (88.5 %; all at the rural center) reported that it did not require effort. The participants reported adopting various lifestyle changes, with some requiring more effort than others. These included removing jewelry, eating more organic fruit and vegetables, changing drinking water, avoiding chemical products, using an alterative toothpaste and deodorant, and changing accommodation.

3.4. Differences at the urban and rural medical centers

Analyses were run to compare the participants at the two medical centers. It was found that the participants were significantly younger at the rural center than at the urban center (31.9 ± 5.4 versus 33.0 ± 5.3 years; $p < 0.0001$); they were also significantly heavier (median 61 kg [inter-quartile range, IQR: 55–66] versus 60 kg [IQR: 55–65], $p < 0.0001$). In addition, most of the participants at the rural medical center were pregnant, but this was not the case at the urban center (79.2 % versus 38.4 %, $p < 0.0001$; see Table 3).

We analyzed the proportion of women with 'risky' levels of exposure to trace metals at the two medical centers. We found that the proportion was higher at the urban medical center than at the rural center (65.1 % versus 54.1 %; see Table 7). However, this was not statistically significant ($\chi^2 = 2.31$; $p = 0.13$). We noted that participants with 'risky' levels for more than three trace metals were all at the urban center (N = 7; see Fig. 2), but this was not found to be statistically significant (Fisher's exact test; $p = 0.27$). We did not analyze differences between the centers for the final hair sample analysis because of the lack of data. However, it was noted that all participants who returned for the final visit were at the rural medical center.

We examined whether there were differences in certain sources of exposure to heavy metals for participants at the two medical centers. It was found that there were more participants with tattoos at the urban center than at the rural center (48.8 % versus 12.7 %, $p < 0.0001$; Table 3). There was no significant difference in the number of participants who smoked (rural center: 21.9 %; urban center: 30.2 %, $p > 0.05$), and at both centers, the vast majority smoked e-cigarettes (rural center: 20/21; urban center: 25/26). However, the number of e-cigarettes smoked per day was significantly lower for the participants at the rural medical center (median: 5 [IQR: 2–10] versus 8 [IQR: 2–10], $p < 0.0001$). There was no significant difference in the number of participants who wore a metallic orthodontic appliance (rural center: 2.1 %; urban center: 1.2 %; $p > 0.05$).

The responses to the living environment questionnaire were analyzed, and they confirmed several expected differences: participants at the rural medical center were more likely to live in a house and near a farm; they consumed more home produce and travelled further to get to work (all $p < 0.0001$; see Table 8). The results also showed that more participants at the rural center had accommodation with new lead-free paint (87.5 % versus 48.8 %; $p < 0.0001$); they also drank more bottled water ($p < 0.0001$) and ate less organic food ($p < 0.0001$).

3.5. Risk factors for 'risky' levels of exposure to trace metals

Univariate logistic regression analyses were run to identify factors that could potentially predict 'risky' levels of exposure to trace metals (see Supplementary Material Table 1). Analyses were run for the participants' demographic and clinical characteristics (e.g., age, weight) and for the living environment questionnaire responses, which included items related to the participants' diet (e.g., organic food, bottled water), their surroundings (e.g., living near a farm), and their work (e.g., distance to work; see Supplementary Material 1). Various factors were identified that could potentially predict 'risky' levels of trace metals ($p < 0.2$): the participants' age ($p = 0.13$), having a tattoo ($p = 0.13$), smoking ($p = 0.10$), taking a vitamin supplement ($p = 0.18$), an urban living location ($p = 0.13$),

Table 5
Changes in the number of 'risky' trace metals at the final visit (post-intervention).

	Fewer trace metals at 'risky' levels	Same number/more trace metals at 'risky' levels	TOTAL
Number of participants (%)	14 (66.7)	7 (66.7)	21 (100)
Initial and final numbers of 'risky' trace metals	1 → 0 (n = 8)	1 → 1 (n = 1)	
	2 → 0 (n = 1)	1 → 2 (n = 1)	
	2 → 1 (n = 3)	1 → 3 (n = 1)	
	3 → 0 (n = 1)	1 → 4 (n = 2)	
	3 → 2 (n = 1)	2 → 2 (n = 2)	

Table 6
Number of times a trace metal initially found to be at 'risky' levels was no longer so in the second hair sample.

Trace metal at 'risky' levels in the first hair sample but not the second sample	Number
Tellurium	5
Nickel	4
Iron	3
Rare-earth elements (other than cerium)	3
Titanium	3
Cerium	2
Silver	2
Strontium	2
Antimony	1
Manganese	1
Mercury	1

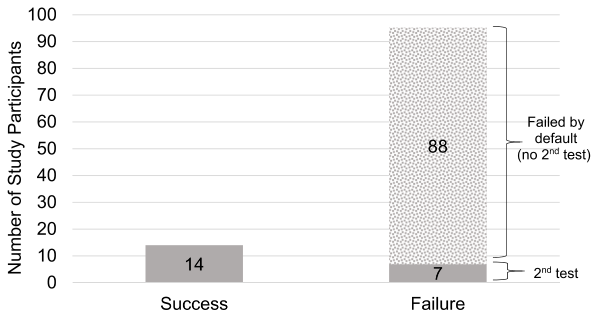

Fig. 4. Number of participants with successfully reduced 'risky' levels of trace metals
Success was defined as a reduction in the number of trace metals at 'risky' levels in the second hair sample compared with the first sample.

Table 7
Number of participants with 'risky' levels of trace metals at the rural and urban medical centers (initial hair sample).

	Rural Center (N = 98)	Urban Center (N = 86)	Total (N = 184)
'Risky' levels	53 (54.1 %)	56 (65.1 %)	109 (59.2 %)
No 'risky' levels	45 (45.9 %)	30 (34.9 %)	75 (40.8 %)
$\chi^2 = 2.31$; p = 0.13			

Table 8
Results from the living environment questionnaire.

	Rural Center (N = 98)	Urban Center (N = 86)	Total (N = 184)	Difference
Median organic food intake (IQR), %	20 [5–50]	30 [10–43,56–62]	22 [10–43,56–62]	P < 0.0001[b]
Median intake of bottled water (IQR), %	45 (0–80)	0 (0–20)	10 (0–50)	P < 0.0001[b]
Median intake of home produce (IQR), %	0 (0–15)	0 (0–0)	0 (0–10)	P < 0.0001[b]
Living in house, N/total N[a]	79/97 (81.4 %)	30/86 (34.9 %)	109/183 (59.6 %)	P < 0.0001[c]
Median building age (IQR), years	12 [5–50]	40 [12–62]	22 [9–52]	P < 0.0001[b]
New paint, N/total N[a]	84/96 (87.5 %)	42/86 (48.8 %)	126/182 (69.2 %)	P < 0.0001[c]
Accommodation <500 m from industrial site, etc., N/total N[a]	29/91 (31.9 %)	33/86 (38.4 %)	62/177 (35.0 %)	P = 0.36[c]
Accommodation near farm, N/total N[a]	36/91 (39.6 %)	12/86 (14.0 %)	48/177 (27.1 %)	P < 0.0001[c]
Median number of hours spent outside each day (IQR)	2 [2–4]	2 [2,3]	2 [2,3]	P < 0.0001[b]
Median distance to work (IQR), km	10 [5–20]	4 [2–10]	8 [2–16]	P < 0.0001[b]
Exposure to pollutants at work, N/total N[a]	29/82 (35.4 %)	14/64 (21.9 %)	43/146 (29.5 %)	P = 0.08[c]

Statistical tests: b: Wilcoxon test; c: chi-square test.
Abbreviation: IQR: inter-quartile range.
[a] The total N indicates the data that were available.

a newly painted interior (p = 0.15), eating home produce (p = 0.13), and the type of workplace (p = 0.18). As the latter two factors were linked to the urban/rural location, these were not included in the final multivariate regression analysis. The analysis was therefore run using the other factors that were identified. The results showed that none of the factors could predict 'risky' levels of trace metals (p > 0.05), although a tendency was observed for tattoos (p = 0.069; see Table 9). These results indicate that the demographic and clinical characteristics as well as the living environment could not predict 'risky' levels of exposure to trace metals in this study.

Table 9
Results of the multivariate logistic regression analysis for factors that could predict 'risky' levels of trace metals.

	Odds Ratios	95 % Confidence Intervals	P	Significance
(Intercept)	0.88	0.06–13.04	0.93	NS
Age	1.02	0.95–1.09	0.57	NS
Tattoo (yes/no)	0.46	0.19–1.05	0.069	NS (tendency)
Smoker (yes/no)	1.44	0.63–3.46	0.40	NS
Taking vitamin supplement (yes/no)	1.27	0.44–3.86	0.67	NS
Living location (rural/urban)	1.28	0.51–3.26	0.60	NS
New paint at home (yes/no)	0.7	0.32–1.52	0.38	NS

4. Discussion

This study found that more than half (59.2 %; 109/184) of the study participants had 'risky' levels of exposure to trace metals, as determined using a hair sample analysis. Most of these participants (58.7 %; 64/109) received advice sheets on how to reduce their levels of exposure. However, few participants returned (N = 21) for a second hair sample analysis. Of these, two-thirds (14/21) were found to have successfully reduced their levels of exposure, including ten subjects who no longer had 'risky' levels for any trace metal. However, a statistical analysis, which included participants who had not returned and were considered to have failed by default, showed that the intervention was not successful for reducing 'risky' levels of exposure to trace metals. For the secondary measure of interest, the data showed that there were more participants at the urban medical center with 'risky' levels of exposure to trace metals than at the rural medical center, but this was not statistically significant.

Most of the participants in this study (59.9 %) were in the first trimester of pregnancy and the others intended to conceive. Given the potentially serious consequences of exposure to certain trace metals *in utero*, such as preterm birth [56] and an increased risk of developing various diseases later in life [22,24], it is therefore concerning that 'risky' levels were seen for over half of the study participants. The metals that were found to have 'risky' levels included mercury (N = 4), which is highly toxic and has been associated with low birthweight and poor neuropsychological/developmental performance [57]. We also identified lead (N = 1), another toxic metal, which is thought to lead to epigenetic modification that could harm long-term health and be passed on to the next generation [58,59].

The metal that was most frequently found to have 'risky' levels was the rare-earth element cerium (N = 26). This metal is found in nanoparticles that are used as fuel additives and in certain polishing products [60], but little is known about its health effects [60,61]. However, there is evidence that it may increase the risk of myocardial infarction [62] and affect the human placenta [63]. The next most frequently identified metal with 'risky' levels was nickel (N = 23), which is an essential trace element in plants, animals, and humans [64]. However, at high concentrations it can be toxic and may lead to organ and tissue damage as well as certain forms of cancer [64,65]. There is also evidence that nickel may be associated with certain birth defects [66,44]. The high levels in our study are therefore a cause for concern.

Although we observed that participants had initially appeared to be eager to participate in the study, a disappointingly low number of participants with 'risky' levels of exposure returned to complete the study. As a result, the intervention was considered to have failed to reduce the participants' levels of exposure. It is important to consider why this may have been the case so that improvements can be made in the future. One possibility relates to the advice that was given. Specifically, it is possible that participants may have considered the recommendations to be too demanding and consequently dropped out of the study. Although 42.1 % (8/19) of the participants who gave feedback reported that it had not been difficult to avoid exposure to the trace metals, this may relate to which metals they were required to avoid. For instance, some advice sheets recommended relatively easy lifestyle changes, such as washing hands after touching a particular metal (e.g., for tin) and avoiding rat poison (for thallium), whereas others contained recommendations that may have been considered extremely difficult, such as stopping smoking (e.g., for cadmium), or too expensive, such as eating organic food (e.g., for aluminum). It is also possible that the advice sheets contained recommendations that went against the participants' beliefs about health risks, such as choosing tap water as opposed to bottled water (e.g., for antimony), as tap water is often perceived as a riskier option [45]. It is also relevant that participants were encouraged to find out about potential sources of exposure themselves for trace metals that did not have a corresponding advice sheet; some participants may have considered this to be too difficult or too time-consuming.

Despite the low completion rates in our study, it is encouraging that of those who did return, the majority were found to have successfully reduced their exposure to trace metals (14/21). However, this result should be interpreted with caution given the small number of participants who completed the study. Further studies are therefore required with larger sample sizes to determine the effectiveness of the intervention. It is also relevant to note that there may have been bias in terms of the participants who returned to complete the study and that this may have affected the results. For instance, those who returned may have been more motivated and compliant, which would have led to higher success rates. This would therefore limit the generalizability of the findings.

We noted that the participants who returned to complete the study were all at the rural center. This may relate to the fact that most of these women were already pregnant, unlike at the urban center (79.2 % versus 38.4 %). As pregnant women in France are required to have a medical consultation every month from the third month of pregnancy, this would have increased the likelihood of them returning to complete the study. Previous work has also shown that women are more likely to give up smoking when pregnant compared to before pregnancy [46]. It is therefore possible that the pregnant women in our study were also more motivated to avoid trace metals, and so were more likely to return to complete the study. An alternative possibility may relate to the fact that women who live in a rural location have fewer medical centers close by and so they may be less likely to change to a different center. Cultural factors may also play a role, such as a tendency to be followed up by the same doctor in rural settings.

Previous studies have investigated factors that could improve rates of compliance with recommended lifestyle changes for pregnant women and those intending to conceive. This has been particularly well studied for smoking cessation, as there are still many women who smoke (31.9 % in France) [47] and there are well-known negative effects on the child, such as an increased risk of low birth-weight, asthma, and behavioral problems [48]. Promising strategies have been identified to help pregnant women to give up smoking, including the use of incentives [49], serious games [50], smartphone apps [51], and behavioral counselling [52]. Such strategies could therefore also be considered for women who would benefit from lifestyle changes to reduce their exposure to harmful trace metals during pregnancy.

In our study, we carried out analyses to identify factors that could predict 'risky' levels of exposure to trace metals. However, despite considering a range of measures, none came out as statistically significant. This is somewhat surprising as we included factors that are well known to be associated with exposure to trace metals, such as smoking [16,53]. However, it is possible that the results were not significant because we did not consider each metal separately, but rather included them all in the same analysis, which may have masked certain associations.

Our study found several statistically significant differences between participants at the rural and urban centers. For example, the participants at the urban center were more likely to have a tattoo, they smoked more e-cigarettes per day, and they were less likely to have new paint at home. However, although these factors are known to be associated with exposure to trace metals [10,12,54], the participants at the urban center did not have significantly more 'risky' levels in their hair samples. It is possible that a significant difference may have emerged with a larger sample size, as the difference between the urban and rural centers was relatively large, at over 10 % (rural center: 54.1 % with 'risky' levels; urban center: 65.1 % with 'risky' levels). However, this remains to be determined in future studies.

The main limitation of our study relates to the lack of follow-up data for the study participants, particularly those at the urban medical center. It will be important to focus on improving this in future studies, possibly by adopting strategies to improve compliance, as described above. It would also be helpful to have a larger sample size. Another limitation relates to the use of hair samples to assess exposure to trace metals. Although this is a convenient and non-invasive option, certain trace metals in the hair are not always found to correlate strongly with concentrations found in the blood and urine (e.g., iron, copper), although this may depend on the particular metal [55]. It would therefore be helpful to have additional biomarkers to detect trace metals in addition to the hair, such as the blood or urine. A further limitation is that differences were not always clear-cut regarding the living environment of the participants at the rural and urban medical centers. For example, several participants at the urban center reported that they lived near a farm, although the percentage was significantly lower than at the rural center (14.0 % versus 39.6 %, $p < 0.0001$). We overcame this to a certain extent through the living environment questionnaire, which analyzed various factors separately. However, it would be interesting to run further studies that include more extreme differences in environmental exposure, for example by including groups from megacities or industrial areas. Another limitation is that this study only included women who were pregnant or intended to conceive. The results may therefore not apply to other populations who may also have 'risky' levels of exposure to trace metals, such as men and older adults. Finally, our study only had advice sheets for nine of the trace metals and it is unclear how much information the participants obtained about other metals at 'risky' levels.

Despite these limitations, our approach has clear benefits. For instance, the hair sample analysis can be used to raise awareness of the dangers of exposure to trace metals during pregnancy and encourage women to adopt behaviors that will protect the long-term health of their children. In this way, women can take proactive steps in protecting their own health as well as that of their children. A further strength of our study relates to the fact that individualized advice was provided, as there is evidence that this can be more effective for changing behavioral patterns [67].

Our study could form a starting point for further research. This could lead to the development of more effective interventions for reducing trace metal exposure. For instance, there are various strategies that could be adopted to motivate and encourage women to avoid trace metals, such as interventions based on smartphone apps. It would also be of interest to determine the benefits of providing individualized advice that considers not only the trace metals at 'risky' levels but also the participants' financial and practical constraints. Over the long term, it may be possible to develop programs that include hair sample analysis and smartphone-based interventions for use in public health programs. This would enable large numbers of pregnant women to avoid harmful trace metals and protect the health of their children.

5. Conclusions

This study showed that a relatively large proportion of women who were pregnant or intended to conceive had 'risky' levels of exposure to trace metals, as determined using a hair sample analysis. Over half of these women received advice sheets on how to reduce their exposure, or if these were not available, they were encouraged to seek out potential sources of exposure. However, few participants returned to complete the study. Of those who did return, two-thirds (14/21) were found to have successfully reduced their exposure to trace metals. These results highlight the need for improved interventions to reduce harmful exposure to trace metals during or prior to pregnancy.

Ethics statement

This study was reviewed and approved by the Committee for the Protection of Persons (North-West II, France), with the approval number: 2020-A01954-35 (December 3, 2020). All participants provided informed consent to participate in the study.

Data availability statement

The data for this study are available from the author upon reasonable request.

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CRediT authorship contribution statement

François Lisik: Conceptualization, Formal analysis, Investigation, Methodology, Validation, Writing – original draft, Writing – review & editing, Resources, Supervision. **Mathilde Piketty-Desfeux:** Investigation. **Christine Tchikladze:** Formal analysis, Supervision, Writing – original draft, Writing – review & editing. **Éric Glowaczower:** Conceptualization, Investigation, Methodology.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2023.e21293.

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