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A cross sectional study of the relationship between the exposure of pregnant women to military attacks in 2014 in Gaza and the load of heavy metal contaminants in the hair of mothers and newborns

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ABSTRACT

Objective Metal contamination of humans in war areas has rarely been investigated. Weaponry's heavy metals become environmentally stable war remnants and accumulate in living things. They also pose health risks in terms of prenatal intake, with potential long term risks for reproductive and children's health. We studied the contribution of military attacks to the load of 23 metals in the hair of Palestinian women in the Gaza Strip, who were pregnant at the time of the military attacks in 2014, and their newborns. We compared the metal load in the mothers with values for adult hair from outside the war area (RHS) as the reference. We investigated heavy metals trans-passing in utero, and assessed if the heavy metal intake could derive from sources unrelated to the war.

Design Cross sectional study.

Participants and setting Cross sectional convenience sample of 502 mothers delivering in the Gaza Strip and their newborns.

Main outcome measured Measure of the load of heavy metals in mother and newborn hair by inductively coupled plasma-mass spectrometry (ICP-MS). Comparison of metal loads with the reference RHS, between groups with different exposures to attacks and house/agriculture chemicals, and between mothers and newborns. Data for birth registry and for exposures to war and other known risk factors were obtained at interview with the mothers. Photographic documentation of damage from military attacks was obtained.

Results The whole cross sectional convenience sample had a significantly higher load of heavy metals than the reference RHS. Women exposed to military attacks had a significantly higher load of heavy metals than those not exposed; the load in newborns correlated positively with the mothers' load. No significant difference was found between users/non-users of house/agriculture chemicals. No other known confounder was identified.

Conclusions High heavy metal loads in mothers, reflected in those of their newborns, were associated with exposure to military attacks, posing a risk of immediate and long term negative outcomes for pregnancy and child health. Surveillance, biomonitoring and further research are recommended. Implications for general and public health are discussed.

Strength and limitations of this study

- The lack of 'never exposed to war' controls within Gaza is a limitation of the study which cannot be overcome.
- A general limitation of this type of study is that the risks posed in the long term by the intake of multiple heavy metals are still largely unknown in humans, and in particular during pregnancy.
- The size of the sample, while adequate to identify the correlation between levels of heavy metals with environmental exposure, is not large enough to accurately study the negative outcomes at birth (birth defects and preterm) due to their low frequency.
- A strength of the study is the inclusion of a relatively large cross sectional convenience sample of participants, allowing for subgroups of exposure, suitable in size for statistical analysis.
- An important point was the inclusion of analyis of newborn hair in for metal load. .
- Verification by in loco visits the recall of exposure of women on an objective basis gives additional strength to the study.
- Development of a questionnaire and of procedures that allowed information to be obtained on various habits and different potentially risky environmental exposures, -allowing to exclude some more likely potential confounders.
- The analysis of microelements and metals not associated with weaponry provided an internal control for the analytic results.

INTRODUCTION

Women and children are highly vulnerable during periods of war and military attacks, as well as in the aftermath of war, because of the possibility of the long term effects of war related environmental changes on reproductive and infant health. Accumulation in human bodies of toxicants and heavy metal teratogens found in the remnants of war occurs, that, coupled with their long persistence in the environment, suggests a considerable risk for health.[1–6] The effects of toxicants, teratogens and carcinogens related to heavy metals have been found in embryos at concentrations lower than in adults.[7 8] During the first trimester of pregnancy, major morphogenetic events occur, and is the period of highest sensitivity of the embryo to external effectors. Apart from the mutational risks posed by some of the heavy metals, there is compelling evidence of their prevalent epigenetic mechanisms of action.[8–15] Heavy metals act as endocrine disruptors,[8] and their interference with gene expression causes disturbances in various metabolic and hormonal pathways.[9] The epigenetic mechanisms are an essential part of the current understanding of the developmental origin of health and disease.[11–15] Reports show that heavy metals accumulate in specific body compartments and can be released during pregnancy.[9 12–15] However, relatively little is known about the kinetics, modalities and accumulation of heavy metals in compartments of the human body. Also, not much is known about the following phenomena: the effects of human subjects' concurrent intake of multiple toxic metals, the kinetics of the passage of heavy metals through the placenta and the critical concentrations that affect the embryo and fetus.

In addition to the risks posed by acute exposure, persistence of heavy metals in the environment may cause people to be continually exposed which, combined with the accumulation of heavy metals in different compartments of the body, adds to the concerns about the long term negative effects on health. The long term effects of metals via epigenetic mechanisms can occur in mothers, fetuses exposed in utero and in breastfed infants and children; these effects could even be transgenerational.[10–13 16 17]

Military attacks are a source of heavy metal input in war zone environments, and may influence the health of the population and affect the outcomes of pregnancies.[4 16] The prevalence of birth defects increased in areas heavily exposed to military attacks in Iraq,[18] and in Gaza after the Israeli military operation of Cast Lead in 2008–2009[19] and since the implementation of air delivered weapons in attacks.[20] Previous research in Gaza also showed that women's exposure to military attacks (courtesy of the database of the United Nations' mine action team) correlated with a higher incidence of progeny with birth defects.[20 21] Hair analysis for metal load of infants born prematurely or with birth defects to mothers who experienced military attacks revealed in utero contamination of the babies. The heavy metal load in these newborns was higher than that of normal newborn babies for teratogens (mercury and selenium) in babies with birth defects and for toxicants (barium and tin) in premature babies.[22] Together, the data show an association of the damage to newborn health with maternal exposure to attacks, and the trans-placental passage of wartime heavy metal remnants from exposed mothers to their progeny in utero.

Three major wars, with their complex consequences for the environment, may have been the single most influential determinant of change in the living conditions and in the demography of Gaza from 2008 to 2014. The context of the current study is the aftermath of the 2014 Israeli military operation 'Protective edge' in Gaza, which lasted for 55 days and had massive effects on civilian life. This operation left widespread structural destruction,[23–28] with physical remnants of war, including components of weapons, shrapnel and missiles, as well as environmentally stable chemical elements and contaminated ruins, throughout the area.[29] The weapons used in these attacks were documented by the United Nations and other reputable sources, and included missiles, mortars, explosive devices and bombs of various sizes, with or without penetrator heads. The content of heavy metals in each weapon differed, and each had a different range of spread, from metres to hundreds of metres or more.[23–29] The Israeli government does not make available a list of weapons used, and all data are directly from United Nations' agencies and independent witnesses on the ground. Removal of explosive war remnants and the debris of demolition began only 6–8 months after the end of hostilities and involved the creation of open air deposits and the reuse of materials from demolished structures. No transfers of debris could be conducted outside the area of the Gaza Strip.[29] Thus any contamination due to the 2014 war remained in the local environment from the time of the attacks throughout the period of our study.

The aim of the study was to investigate whether there were changes in the metal load of a representative segment of the female population after military attacks, particularly with respect to heavy metal contaminants with known teratogen, toxicant and carcinogenic effects, which could pose long term risks for health because of their stability in the environment and tendency to accumulate in the human body. We investigated the extent of exposure to attacks in a cross sectional convenience sample of women who had been in their first trimester of pregnancy during the attacks in the summer of 2014 and who entered one of four major maternity hospitals in Gaza for delivery. The correlation between maternal contamination and their newborns' was also investigated.

METHODS

Participants

Participants were 502 mothers who were in their first trimester of pregnancy during the 2014 war on Gaza and who delivered between late January and March 2015 in one of four maternity wards: Al-Shifa (n=202), Al-Awda (n=100), Al-Nasser (n=100) and Al-Aqsa (n=100). All participants were residents in one of four Gaza Strip governorates. There were no exclusion criteria at enrollment; no participant data were discarded after the interviews, and all donated hair samples were analysed.

Procedures

One midwife in each hospital registered all the deliveries occurring during her work shift and obtained the participants' written informed consent for participation in the study. The midwife collected the hair samples from mothers and newborns. The midwife also administered a face to face interview with the mothers, following a prepared questionnaire.[20–22] This included the standards of European and US birth registers and was integrated previously to include the health history of the extended family (to the second degree), and questions about environmental exposure, including the mothers' recollections of their exposures to military attacks and a variety of potentially risky habits. This questionnaire was thus an apt tool for the surveillance of changes in reproductive health, including of the inherited component of newborn congenital diseases, and it was useful for establishing correlations with major environmental changes in Gaza. The Palestinian Health Research Council and the Helsinki Committee for Ethical Approval approved the study. The Research Board in the Islamic University of Gaza, Palestine, reviewed and approved the research tools and procedures. Mothers' recollections of their exposures to attacks were corroborated with objectively documented damage to their dwellings, if the women reported the attacks occurring while they were at home.

Measures

In the present study, the metal load in the hair of mothers and newborns was determined by inductively coupled plasma-mass spectrometry (ICP-MS) using the methodology recommended by the International Atomic Energy Agency (IAEA) for testing human exposure to environmental metals.[30] We analysed women's and newborns' hair for the metal components of weaponry already identified in 2009 at weapons' wound sites in the bodies of victims of attacks.[6] We had also detected these metal components contaminating the hair samples of 65 of 95 children tested 1 year after the attacks of Cast lead (Manduca, unpublished data). We also found some of these metals contaminating the hair of newborns in 2011.[21 22] Finally, we tested 23 metals, including known weapon components and war remnants, such as lead (Pb), barium (Ba), mercury (Hg), arsenic (As), zinc (Zn), cadmium (Cd), tin (Sn), uranium (U), tungsten (W) and aluminium (Al). As an internal control, we also measured other metals and microelements that have biological relevance but are not weapons related.

We compared the metal load of thecross sectional convenience sample of Gaza women with values for adult hair from outside the war area (RHS).[31] We analysed whether the metal loads in mothers were correlated with those in newborns.

Heavy metal concentrations are expressed as ppm (parts per million). Maternal hair (4 cm) was taken nearest to the scalp at the nape of the neck, which reflected environmental exposure during the last 4–5 months of pregnancy and the eventual release of metals previously accumulated in the body. Hair from newborns reflected the accumulation of metals through life in utero.

All hair was preserved in plastic bags until the moment of analysis, according to the recommendations of the IAEA, in the Pacific Rim Laboratory, ISO/Tec 17250 accredited (Canada). Analytical procedures were performed according to previous protocols.[19] In brief, 0.2 g of washed hair was added to 2 mL of HNO_3 and 2 mL of H_2O_2, heated to 85°C for 2 hours and added at room temperature to 6 mL of water. Samples were run in Agilent 7700. The limits of detection (ppm) were: aluminium (Al) and iron (Fe) 0.4; magnesium (Mg), copper (Cu), lead (Pb), manganese (Mn) and titanium (Ti) 0.04; barium (Ba), cobalt (Co) and chromium (Cr) 0.02; arsenic (As), cesium (Cs) and molybdenum (Mo) 0.001; cadmium (Cd) and uranium (U) 0.0001; mercury (Hg) 0.0004; nickel (Ni) 0.15; selenium (Se) 0.22; tin (Sn) and tungsten (W) 0.03; strontium (Sr) 0.01; vanadium (V) 0.002; and zinc (Zn) 0.3. Experimental values below the limits of detection for each metal were considered equal to 0 0 for the purposes of statistical analysis, which was conducted using median values. Commercial analytical standards of hair for calibration purposes were run in parallel (NCS ZC 81002b and NCS DC73347a; China National Analysis Centre for Iron and Steel).

Exposure to military attacks

The variable exposure of women to military attacks was indicated by self-reporting and verified by photographic documentation. Women responded 'yes' or 'no' to five questions: whether their own house was bombed during the 2014 war, whether the house next door was bombed during the 2014 war, whether they were inside their home at the time of the attack, whether they were displaced afterwards and whether they found spent ammunition inside their dweling. Based on these answers, they were grouped according to their 'proximity of exposure to attacks'. The concept of proximal exposure was formulated on the realisation that attacks very often involved the spread of weapons' parts to adjacent houses. The term 'proximally exposed" was used to identify women whose homes or neighbouring homes were attacked. The proximally exposed group was divided into two subgroups according to their continuous habitation in the places where the attacks occurred: women who remained in or next to the house that had been bombarded or shelled, and women who moved elsewhere at some time after the attack. Creation of these subgroups reflects the concern that women with ongoing residence at the locations of the attacks might have had different exposures to war remnants than those who had moved. This concern was, ultimately, unfounded. A third group included women who had no recollection of any exposure. In October 2015, we visited the women in subgroups 1 and 2 and photographically documented the damage that had occurred during the military attacks on their dwellings.

Exposure to potential civilian sources of metal contamination

We tested whether other known potential sources of contamination by heavy metals correlated with the mothers' distribution of metal load. Women were asked about their own use of agricultural substances (pesticides, herbicides, fungicides) and generic household chemicals of unknown composition, their consumption of three main types of medicines and of three prenatal prevention supplements, their use of three available sources of water for drinking and cooking, their frequency of eating fish and their history of smoking. For statistical analyses, a dichotomy variable was formed with 1=women reporting the use of agricultural and household chemicals and 2=non-users.

Statistical methods

The metal loads (ppm) found in the hair of mothers, reported as median values and interquartile ranges, were statistically compared. The first analysis involved the 95th percentile values of the whole cohort and of each exposure group compared with those values for the hair from adults of both sexes from areas unaffected by war (RHS, Germany, by Micro Trace Minerals, MTM; USA by Trace Minerals International, TMI).[31] No equivalent reference was available for the newborns' metal load. The second analysis compared the metal loads within the cross sectional convenience sample between groups proximally exposed and unexposed to military attacks. The third analysis compared the metal loads between users and non-users of agricultural and household chemicals.

In analysing the findings in this study, quantile regression analysis was used because it allowed for the modelling of any percentile or quartile of the outcome, represented in this study by metal distribution, including the median. Furthermore, the Shapiro–Wilk and Pearson's χ^2 normality tests showed that metal concentrations were not normally distributed, and log transformation did not lead to satisfactory results. Quantile regression analysis has the advantage of being more robust against outliers in the outcome variables than least squares regression (linear) and, as a semi-parametric tool, it avoids assumptions about the parametric distribution of the error process.

The relationships between 23 metal concentrations and exposures to military attacks were analysed by multiple quantile regression models, least absolute value models (LAV or MAD) and minimum L1 norm models.[32] The quantile regression models, fit by QREG STATA COMMAND, express the quantiles and the conditional distribution as linear functions of the independent variables which, in this case, are exposure and any confounders. Spearman correlations were used to identify the associations between mothers' and newborns' metal concentrations. All analyses were performed using STATA v.13.

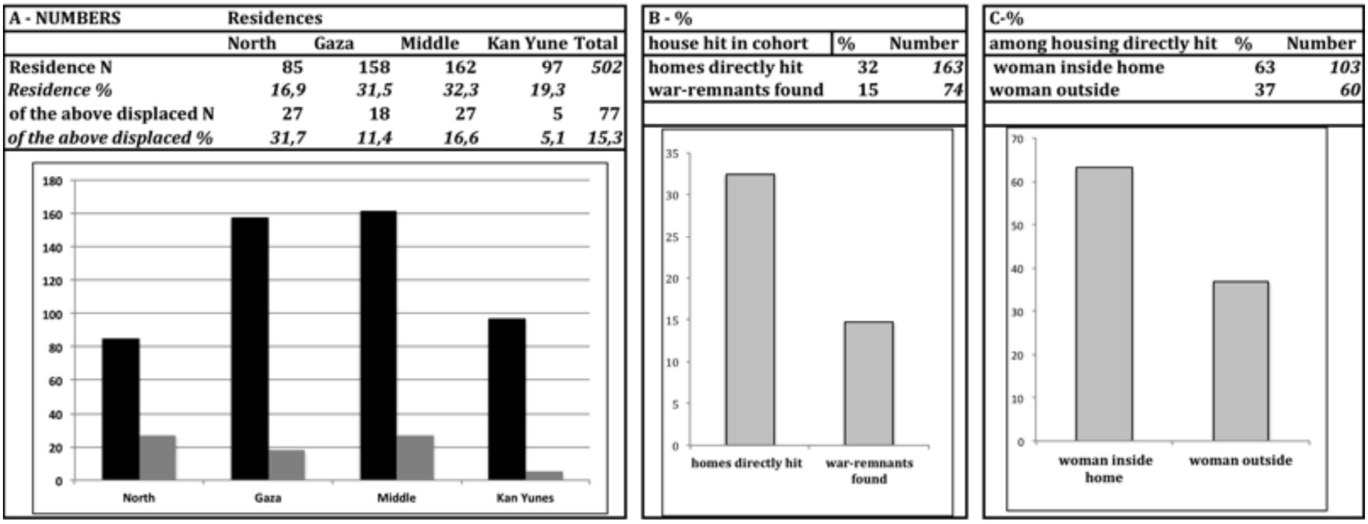
RESULTS

In this sample, median age of the women was 26.9±5.92 years (range 16–52), and 2.5% of participants were younger than 18 years. Of the 502 women, 26.7% were carrying their first pregnancy during the war, and the majority (88.8%) worked at home. Prenatal care efforts, including consumption of iron, vitamins and folic acid, were undertaken by 89% of women. A total of 29% reported a diagnosis of anaemia while 0.5% reported a diagnosis of diabetes. The prevalence of preterm delivery was 1.5%; the prevalence of low birth weight (<2.5 kg) was 2.3%. Of the infants in the study, 4.5% were born with birth defects, and all were born alive, although one baby died in the minutes after birth.

Figure 1A shows the percentages of participants residing in each of the four governorates and whether they were displaced after the military attacks. Information about the exact locations of displacement was not available. Figure 1B shows that 32.4% of women reported weapon hits directly on their own house and 14.7% found war remnants inside the dwelling. Among women whose houses were directly hit (n=163), 63% (n=103) were inside the house during the military attack (Figure 1C). Thus a fifth (20.4%) of all women were in their own home under the attack, and almost half (46.6%) of these found war remnants, generally shrapnel and shells, inside their houses. In addition, 11.9% of the women whose houses were not directly hit reported that weapons remnants reached the interior of their home from military attacks to neighbouring buildings, suggesting a wide radius of the spread of fragments from the blasts.

In October 2015, 78 women of the 103 whose homes were hit while they were inside were contacted, and the damage to 49 homes was recorded (in photographs) in order to objectively document the military attacks. Figure 2A shows the number of the visited homes whose damages were photographed ; of these 63% still exhibited the damage from the attacks. Ten houses were totally destroyed, 15 exhibited major damage and 24 displayed minor damage (Figure 2B and Figure 1 in the online supplement).

Subgroups for personal exposure to military attacks were generated in order to investigate associations between the load of metals in women's hair and their proximity to the military attacks. Figure 3 shows the distribution of the two proximally exposed and the unexposed subgroups. Of the 502 women in this study, 55.9% (n=282) belonged to the subgroup of women who were exposed to an attack and who remained in the same house, where weapon remnants were likely to be present, during the following months of their pregnancy. Subgroup 2, composed of women who were exposed to attacks and who had moved away from the bombed or shelled home, included 12.3%



A - NUMBERS	Residences				
	North	Gaza	Middle	Kan Yune	Total
Residence N	85	158	162	97	502
Residence %	*16,9*	*31,5*	*32,3*	*19,3*	
of the above displaced N	27	18	27	5	77
of the above displaced %	*31,7*	*11,4*	*16,6*	*5,1*	*15,3*

B - %		
house hit in cohort	%	Number
homes directly hit	32	*163*
war-remnants found	15	*74*

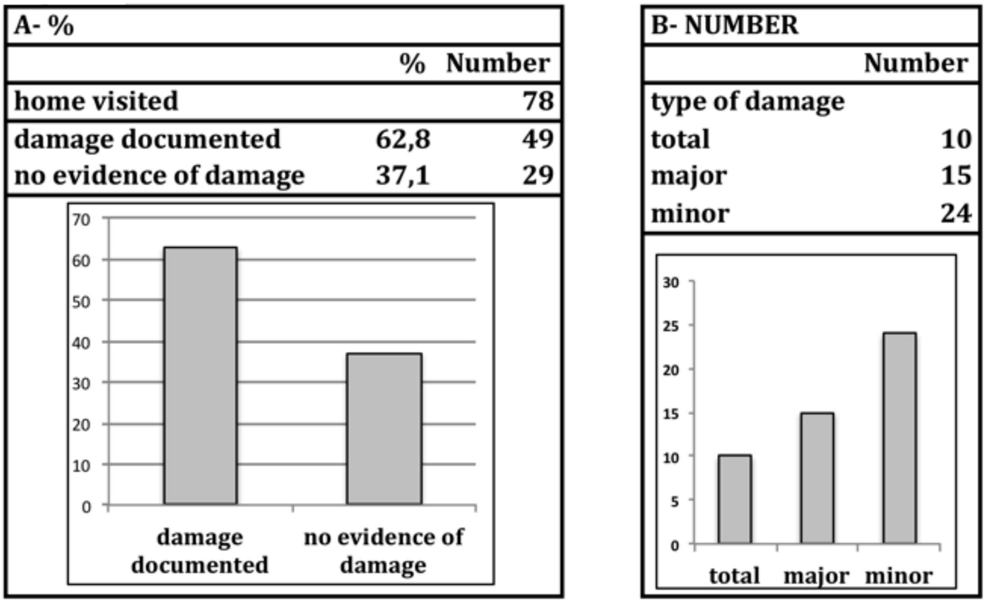
C-%		
among housing directly hit	%	Number
woman inside home	63	*103*
woman outside	37	*60*

Figure 1 -C Localization of the mothers during attacks. (A) The residence of the 502 mothers. In black those residing in late 2015 in the same place as during the attacks in gray those displaced afterwards. (B) Left column, percentage of women in the 502 cross sectional convenience sample that reported that their own housing was hit directly and right column, those that found parts of ammunitions in their house. (C) Percentage of women that were inside their house under the attack .

(n=61) of participants. Subgroups 1 and 2 compose what we named the "proximally exposed" women and were the 68.2% of the cross sectional convenience sample. Approximately one-third (31.7%, n=159) of the women belonged to subgroup 3, who reported not having been under or next door to military strikes and were therefore considered unexposed. Photographic evidence confirmed the damage to the houses of 25 women in subgroup 1 and of 24 women in subgroup 2.

Metal load in mothers and newborns

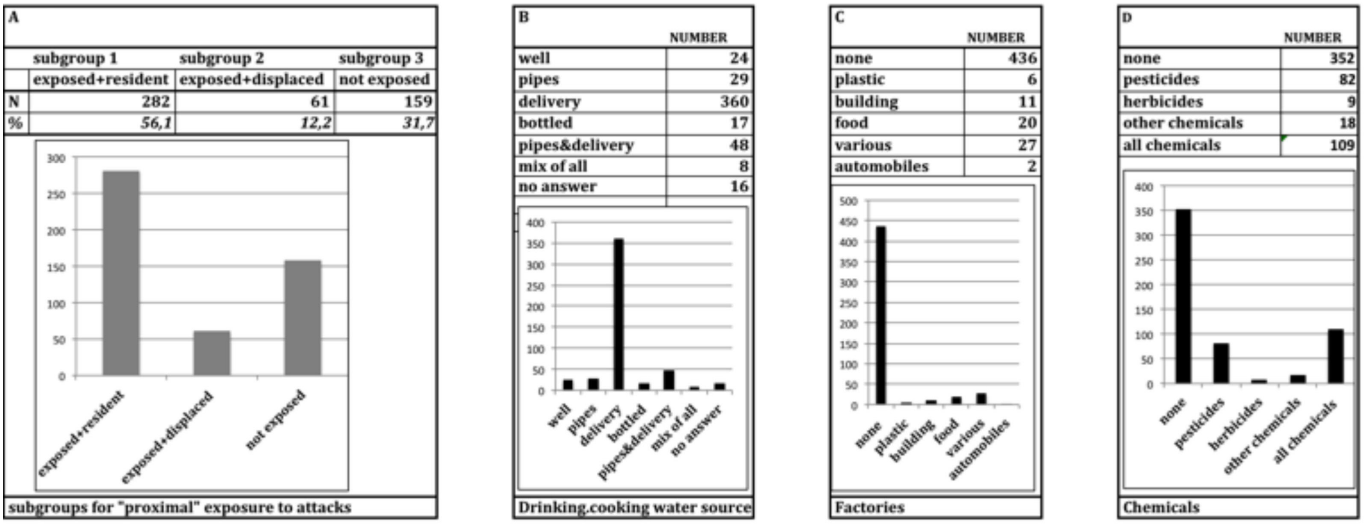
Supplementary Table 1 (see online supplementary Table 1) shows the descriptive values of the metal load, as determined by ICP-MS, for the 23 metals investigated in the hair of mothers and newborns, both for the whole group and for subgroups of exposure to military attacks. In general, the mothers' metal loads were higher than the newborns'. Spearman correlations of the metal load between the mothers and newborns for the whole sample (Table 1) showed significant ($p<0.05$) positive correlations for all metal loads, except for Cu and Sn, and a negative correlation for Ba. These data indicate trans-placental passage of



A- %		
	%	Number
home visited		78
damage documented	62,8	49
no evidence of damage	37,1	29

B- NUMBER	
	Number
type of damage	
total	10
major	15
minor	24

Figure 2 A-B Reported attacks on the housing of the women in the cross sectional convenience sample (n=502). (A) Seventy eight of the 103 women who experienced a direct attack on their house while they were inside it were visited in October 2015. The damages that were still visible were documented by photography. (B) Damages observed classified according to their impact on the structure.



A

	subgroup 1	subgroup 2	subgroup 3
	exposed+resident	exposed+displaced	not exposed
N	282	61	159
%	*56,1*	*12,2*	*31,7*

subgroups for "proximal" exposure to attacks

B

	NUMBER
well	24
pipes	29
delivery	360
bottled	17
pipes&delivery	48
mix of all	8
no answer	16

Drinking.cooking water source

C

	NUMBER
none	436
plastic	6
building	11
food	20
various	27
automobiles	2

Factories

D

	NUMBER
none	352
pesticides	82
herbicides	9
other chemicals	18
all chemicals	109

Chemicals

Figure 3 A-D Distribution of the cross sectional convenience sample according to different environmental exposures. (A) Division of the whole sample into subgroups was based on their reported proximal exposure or non-exposure. All women who reported that their home or the home next door was hit in an attack are in subgroup 1 (55.9% of the sample if they remained a resident in the same house until they delivered their baby, or in subgroup 2 (12.3% of the sample) if they were displaced after the attack. Subgroup 3 (31.7% of the sample reported no exposure to attacks. (B) Source of water for drinking and cooking. (C) Nearness to manufacturers and workshops. (**D**) Use of household and agriculture chemicals (shown in detail): users, or users of any of these chemicals or more than one.

toxicants Cr, Cs, Mo, Ni, Sr, Pb and V, and teratogens Hg, U and W.

The metal load comparison to a reference standard (RHS) from areas unaffected by war (Table 2) shows the comparison of the 95th percentile of the metal load for the mothers with that of RHS. In the whole sample and in each subgroup, the load of toxicants (Al, Fe, Ba, Mn, Ni, Pb, Sr and V), teratogens (Hg, U and W), carcinogens (As, Cd and Co), and of Mg and Zn was significantly higher in the hair of women in all groups of the Gazacross sectional convenience sample than in the reference group RHS. The load of Cs, Cu, Mo, SE, Sn and Ti did not significantly differ from what was found in the reference group, RHS.

Proximal exposure to military attacks and metal load

To examine whether there is an association between proximal exposure to military attacks and metal load, the median values of the subgroups were analysed by multiple quantile regression models. Results showed that both subgroups of proximally exposed women had significantly higher loads for the majority of metals than the unexposed subgroup. For the sake of clarity, Table 3 does not include the following metals which were detected at the same level in all samples as in RHS, and thus unrelated to differences in anthropogenic activities of any kind in the samples and the reference: Cs, Cu, Mo, Se, Sn and Ti. This analysis confirms that proximal exposure is associated with a higher load of contamination for most metals, with an exception for U, with the highest load in subgroup 3. Specifically, subgroups 1 and 2 together showed significantly higher metal loads than subgroup 3 for Al, Mg, Mn, Ba, As, Zn and V. Subgroups 1 and 2 showed significant differences between them: subgroup 1 was highest for Ba and V; subgroup 2 for Cr, Sr and W. Measured loads of Fe, Hg and Pb were higher in the three subgroups than in RHS but did not differ among the subgroups.

Comparison between the newborns groups for metal load showed that the newborns in subgroup 2 had a significantly higher load of contaminants for most metals, except for Hg and Zn. Yet, children in subgroup 3 had a significantly higher load for Al than newborns in subgroup 1.

Regarding exposures to environmental chemicals from civilian sources and potential confounders, the study showed high homogeneity in the women's sample for exposure to most of the potential risk factors. For 84% of the women, it was common to use multiple sources for drinking water, and 87% of the women resided far from industrial plants (figure 3B and C). All of the women used a combination of the five food sources (UNRWA, Egyptian, Israeli and Turkish imports, and local). Less than 5% of women engaged in potentially risky habits, such as smoking, using hair dye or consuming medicines (not shown), and most of the women (90%) ate fish, a potential source of mercury, less than or equal to once per month. These putative risk factors do not seem relevant to the differences in the distribution of the metal load found between the women proximally exposed to military attacks and unexposed women.

Figure 3D shows that 76.3% (n=352) of women reported non-use of household and agricultural chemicals, whereas the 109 women classified as users reported using pesticides (n=82), herbicides (n=9) or other household chemicals (n=18). The chemicals were identified according to their function rather than their chemical composition and were studied only from the point of view

Table 1 Correlation between mothers' and newborns' metal loads. Spearman analysis of the correlation between mothers' and newborns' metal loads. Values of $p<0.05$ are enhanced in yellow for the positive correlations for Mg, Cr, Cs, Hg Mo, Ni, Sr, U, V and W. The correlation is negative for Ba. Values are reported in ppm

Metal*		Whole sample	Exposure 1	Exposure 2	Exposure 3	Metal		Whole sample	Exposure 1	Exposure 2	Exposure 3
Al	n	495	278	59	158	Mo	n	505	282	61	162
	rho	0.0486	0.0554	0.0764	0.0899		rho	0.1182	0.1403	0.0883	0.08
	p	0.2801	0.3576	0.5651	0261		p	0.0078	0.0184	0.4988	0.3113
Fe	n	506	282	61	163	Ni	n	469	270	51	148
	rho	0.0308	−0.0321	0.1373	0.0664		rho	0.1405	0.0646	0.3296	0198
	p	0.4894	0591	0.2913	0.4001		p	0.0023	0.2904	0.0182	0.0159
Mg	n	501	279	61	161	Pb	n	476	271	54	151
	rho	0.1443	0.1512	0.1295	0106		rho	0.0513	−0.0114	0.0104	0.1881
	p	0.0012	0.0115	0.3198	0.1807		p	0.2641	0.8519	0.9406	0.0207
Mn	n	483	275	56	152	Se	n	467	269	50	148
	rho	0.0307	0.0798	−0.0272	−0.0775		rho	0.0381	0.0016	−0.1302	0.1343
	p	0.5005	0187	0842	0.3429		p	0.4115	0.9794	0.3674	0.1036
Ba	n	496	278	61	157	Sn	n	472	271	52	149
	rho	−0.0486	0.0569	−0.1084	−0.1611		rho	0.0156	0017	−0.0064	0.0212
	p	0.2796	0.3447	0.4057	0.0438		p	0.7352	0781	0964	0.7972
As	n	499	281	61	157	Sr	n	505	282	61	162
	rho	0038	0.0408	0.06	0.0543		rho	0.2308	0.2857	0.0931	0.1289
	p	0.3973	0.4953	0.6462	0.4991		p	0	0	0.4753	0.1021
Cd	n	503	281	61	161	Ti	n	496	278	58	160
	rho	−0.0351	−0.027	−0.2051	0.0297		rho	0.0527	0.0196	−0.0437	0.1522
	p	0.4317	0.6517	0.1129	0.7083		p	0.2416	0.7444	0.7444	0.0547
Co	n	468	269	50	149	U	n	493	278	59	156
	rho	−0.0849	−0.0961	−0.0334	−0.0645		rho	0.1398	0.1608	0.2142	0055
	p	0.0666	0.1158	0.8179	0.4347		p	0.0019	0.0072	0.1032	0.4952
Cr	n	480	273	54	153	V	n	482	275	51	156
	rho	0.1105	0.0915	0.1661	0.0984		rho	0.0938	0.1043	0.0953	0.0806
	p	0.0154	0.1316	0.2299	0.2261		p	0.0396	0.0843	0.5059	0.3174
Cs	n	474	272	52	150	W	n	491	277	59	155
	rho	0.1789	0.1904	−0.1259	0.2293		rho	0.4594	0.4288	0.6026	0.3253
	p	0.0001	0.0016	0.3738	0.0048		p	0	0	0	0
Cu	n	505	282	61	162	Zn	n	505	282	61	162

Continued

Table 1 Continued

Metal*		Whole sample	Exposure 1	Exposure 2	Exposure 3	Metal		Whole sample	Exposure 1	Exposure 2	Exposure 3
	rho	0.0031	0.0313	−0.0912	−0.0032		rho	0.0385	0.0768	−0.1213	0.0258
	p	0.9451	0.6008	0.4847	0.9681		p	0.3883	0.1984	0.3517	0.7446
Hg	n	505	282	61	162						
	rho	0.2135	0.2051	0.1798	0.2282						
	p	0	0.0005	0.1655	0.0035						

*Al, aluminium; Fe, iron; Mg, magnesium; Mn, manganese; Ba, barium; As, arsenic; Cd, cadmium; Co, cobalt; Cr, chromium; Cs, cesium; Cu, copper; Hg, mercury.

of their potential contribution to the load of heavy metals in hair. Table 4 compares the median quantiles between user and non-user groups, showing no significant differences (p >0.3 for all analyses) among these subgroups in the load for all 23 metals. It is possible, then, to rule out the possibility that the use of these products contributed to the heavy metal contamination.

DISCUSSION

Principal findings

The study is the first to document the number of civilian subjects in the population who were exposed in 2014 to military attacks in Gaza. The women in this cross sectional convenience sample experienced, in 32.4% of cases, a direct hit to their private dwellings and, in 63% of these cases, the attacks occurred while the women were inside their homes. The women's recollections were supported by photographic documentation of the reported damage which verified its extent. Hits including those on neighbouring buildings (proximal exposure) were reported by almost 70% of the women.

The study examined the load of heavy metals in the hair of this cross sectional convenience sample of women who were all pregnant during the war in Gaza in 2014. Hair samples were collected when the women delivered during the winter of 2014 and the spring of 2015. We found a positive correlation between a high load of toxicants (Ba, Al, V, Sr and Cr), a teratogen (W) and a carcinogen (As) in women's hair and their proximity to military attacks in 2014.

We also found that there was a higher load in the entire cross sectional convenience sample of Gaza women in comparison with the hair samples from individuals in areas unaffected by war (RHS), regardless of their recent exposure to attacks. The high load was for heavy metals already detected as war remnants from previous attacks in 2009 (toxicants such as Al, Fe, Ba, Mn, Cr, Ni, Pb, Sr and V; teratogens such as U and W; and carcinogens such as As, Cd and Co).

There was, instead, no difference in the cross sectional convenience sample of Gaza women, regardless of their reported exposure to the attacks in 2014, in comparison with the metal load in the hair of adults of both sexes from the areas unaffected by war (RHS) for the concentration of microelements (Cu, Se and Mo) and a few other metals (Cs, Sn and Ti). Moreover, anthropogenic sources not arising from military attacks were excluded as confounders. These data confirm that the source of toxicant, teratogen and carcinogen contaminants was anthropogenic and associated with military attacks. We also showed that there was trans-placental passage for heavy metals from mothers to their newborns.

Limitations of the study

The lack of 'never exposed to war' controls within Gaza is a limitation of the study which cannot be overcome because there is no recent 'time zero' for anthropogenic,

Table 2 Comparison of the metal load of the mothers in the cross sectional convenience sample and in subgroups 1, 2 and 3 with that of reference ranges of standards from areas not involved in the war. Comparison of the 95th percentile of metal load in the wholesample and in subgroups 1–3 with that of standards from areas not involved in wars. Confidence intervals are shown. Results with 95th percentiles significantly higher than the reference value are enhanced in light blue and in bold. Values are reported in ppm. Subgroups 1 and 2 are mothers 'proximally exposed' to attacks and subgroup 3 those that reported no exposure

	All mothersl (n=502)			Exposure group 1 (n=282)			Exposure group 2 (n=61)			Exposure group 3 (n=159)			Reference value
Metal*	**95th percentile**	**95% CI**		**95th percentile**	**95% CI**		**95th percentile**	**95% CI**		**95th percentile**	**95% CI**		**95°percentile**
Al	**16.91**	13.88	21.68	**15.37**	13.06	21.63	**15.60**	12.60	47.60	**18.87**	13.57	25.11	**<8**
Fe	**40.16**	35.25	52.28	**41.07**	34.50	55.07	**35.52**	26.49	418.33	**40.26**	34.52	68.23	**1.6–17**
Mg	**1260.00**	1260	1123	**1198**	1108	1381	**1265.00**	1012.27	1130	**1510**	1057.	1745	**20–130**
Mn	**2.90**	2.38	3.44	**2.87**	2.28	3.40	**4.52**	1.89	13.20	**2.99**	2.18	4.76	**0.05–0.92**
Ba	**29.69**	24.04	49.18	**42.52**	26.98	137.13	**22.07**	15.13	33.90	**20.10**	15.46	53.45	**<4.64**
As	**0.24**	0.21	0.28	**0.23**	0.20	0.28	0.28	0.14	0.38	**0.25**	0.21	0.50	**<0.2**
Cd	**0.24**	0.20	0.30	0.20	0.18	0.30	0.25	0.19	0.47	**0.28**	0.20	0.37	**<0.2**
Co	**0.57**	0.37	0.76	**0.75**	0.50	1.04	0.57	0.24	0.72	0.32	0.22	0.69	**0.01–0.30**
Cr	**2.93**	2.43	3.29	**2.28**	2.10	2.97	**3.95**	2.79	7.52	**3.20**	2.64	3.74	**0.02–0.21**
Cs	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	**<0.01**
Cu	40.73	33.60	52.24	48.53	37.72	71.78	35.67	23.63	145.00	31.10	27.51	62.63	**Oct-41**
Hg	**1.62**	1.16	4.84	**1.50**	0.97	3.14	**20.61**	0.95	2480.00	**1.41**	1.08	24.20	**<0.60**
Mo	0.26	0.21	0.32	0.23	0.18	0.30	0.40	0.25	0.78	0.28	0.20	0.38	**0.03–1.00**
Ni	**2.76**	2.23	3.56	**2.76**	2.23	3.90	**2.05**	1.69	3.31	**3.10**	2.05	4.51	**<1.00**
Pb	**6.50**	6.00	7.35	**6.65**	6.17	7.98	**6.47**	3.77	7.25	**6.17**	5.25	9.67	**<3.0**
Se	0.88	0.86	0.95	0.87	0.83	0.95	0.99	0.84	8.47	0.89	0.87	0.97	**0.40–1.70**
Sn	0.75	0.61	0.98	0.75	0.57	1.04	0.86	0.49	1.94	0.71	0.55	1.09	**<0.70**
Sr	**136.00**	122.39	160.26	**134.85**	118.00	162.53	**161.50**	113.66	1480.00	**142.00**	108.46	197.21	**0.65–6.90**
Ti	0.82	0.73	1.00	0.76	0.70	1.01	0.72	0.51	1.45	0.89	0.69	1.15	**<1.50**
U	**0.53**	0.46	0.68	**0.46**	0.40	0.62	**0.71**	0.48	2.49	**0.65**	0.48	1.01	**<0.10**
V	**1.40**	1.26	1.56	**1.27**	1.16	1.40	**1.88**	1.39	3.92	**1.56**	1.25	1.80	**0.01–0.20**
W	**1.37**	1.07	2.28	**1.76**	1.06	2.74	**2.48**	1.20	7.27	**0.99**	0.48	1.52	**<0.02**
Zn	**990.5**	902.2	1202,8	**1029.6**	889.7	1269	**990.1**	767.3	1657.1	**926.53**	671.20	1569.16	**150–272**

*Al, aluminium; Fe, iron; Mg, magnesium; Mn, manganese; Ba, barium; As, arsenic; Cd, cadmium; Co, cobalt; Cr, chromium; Cs, cesium; Cu, copper; Hg, mercury; Mo, molybdenum; Ni, nickel; Pb, lead; Se, selenium; Sn, tin; Sr, strontium; Ti, titanium; U, uranium; V, vanadium; W, tungsten; Zn, zinc.

Table 3a Comparison between mothers of metal load between subgroups according to their 'proximal exposure'. The metal load in mothers from different subgroups were compared with each other. Analysis was by multiple quantile regression on median values as linear function of the independent variable, 'proximal exposure'. For ease in reading the data, the colour yellow indicates that the group in the first column of each panel has significantly higher load (p<0,05) than the one in the second column of the same panel. If vice versa, the line is enhanced in green colour. Panel A compares exposure subgroups 1 with 3; panel B compares exposure subgroups 1 with subgroups 2+3

Mother								
A								
Metal	**Median exposure 1**	**95% CI**	**Median exposure 3**	**95% CI**	**Difference**	**p>|t|**	**95% CI - INF**	**95% CI -SUP**
Al	6.1	5.59 to 6.61	5.17	4.49 to5.85	0.9299998	0.032	0.0813438	1.778656
Fe	14.26	13.33 to 15.19	14.76	13.52 to16	−0.5	0.527	−2.053229	1.053229
Mg	518	476.47 to 559.53	436	380.7 to491.3	82	0.02	12.8438	151.1562
Mn	0.77	0.69 to 0.85	0.58	0.48 to0.68	0.19	0.004	0.0594475	0.3205525
Ba	5.45	4.62 to 6.28	3.79	2.69 to4.89	1.66	0.018	0.2801481	3.039852
As	0.077	0.07 to 0.08	0.059	0.05 to0.07	0.018	0.007	0.0048824	0.0311176
Cd	0.0466	0.04 to 0.05	0.0429	0.03 to0.05	0.0037	0.537	−0.0080632	0.0154632
Co	0.05	0.04 to 0.06	0.04	0.03 to0.05	0.01	0.087	−0.0014529	0.0214529
Cr	0.67	0.59 to 0.75	0.58	0.47 to0.69	0.09	0.2	−0.0477462	0.2277463
Cu	12.7	11.88 to 13.52	12.8	11.71 to13.89	−0.1000004	0.885	−1.463699	1.263698
Hg	0.188	0.16 to 0.22	0.198	0.16 to0.24	−0.01	0.677	−0.0571568	0.0371568
Ni	0.65	0.56 to 0.74	0.46	0.34 to0.58	0.19	0.01	0.0461767	0.3338233
Pb	1.59	1.32 to 1.86	1.43	1.07 to1.79	0.1600001	0.479	−0.2842991	0.6042993
Sr	48	44.06 to 51.94	45.4	40.16 to50.64	2.599998	0.436	−3.953596	9.153592
Ti	0.27	0.24 to 0.3	0.22	0.19 to0.25	0.05	0.024	0.0066297	0.0933703
U	0.13	0.11 to 0.15	0.177	0.15 to0.2	−0.047	0.003	−0.0779462	−0.0160538
V	0.453	0.4 to 0.51	0.291	0.22 to0.37	0.162	0.001	0.0682058	0.2557942
W	0.03	0.03 to 0.03	0.03	0.02 to0.04	0	1	−0.0076353	0.0076353
Zn	296.93	270.11 to 323.75	250.72	215 to286.44	46.20999	0.043	1.542475	90.87751
B								
Metal	**Median exposure 1**	**95% CI**	**Median exposures 2+3**	**95% CI**	**Difference**	**p>|t|**	**95% CI - INF**	**95% CI -SUP**
Al	6.1	5.57 to 6.63	5.32	4.72 to5.92	0.7799997	0.058	−0.0268346	1.586834
Fe	14.26	13.29 to 15.23	14.9	13.81to 15.99	−0.6399994	0.389	−2.099536	0.8195368
Mg	518	475.04 to 560.96	480	431.36 to 528.64	38	0.25	−26.89435	102.8944
Mn	0.77	0.68 to 0.86	0.66	0.56 to 0.76	0.11	0.106	−0.0232821	0.243282
Ba	5.45	4.65 to6.25	3.62	2.71 to 4.53	1.83	0.003	0.6196477	3.040352
As	0.077	0.07 to0.08	0.062	0.05 to 0.07	0.015	0.012	0.0033205	0.0266795

Continued

Table 3a Continued

Cd	0.0466	0.04 to0.05	0.0421	0.03 to 0.05	0.0045	0.411	−0.0062438	0.0152438
Co	0.05	0.04 to0.06	0.04	0.03 to 0.05	0.01	0.034	0.0007411	0.0192589
Cr	0.67	0.57– to 0.77	0.64	0.53 to 0.75	0.03	0.687	−0.1161984	0.1761984
Cu	12.7	11.87 to 13.53	12.6	11.66 to 13.54	0.0999994	0.875	−1.14916	1.349159
Hg	0.188	0.16 to 0.21	0.189	0.16 to 0.22	−0.001	0.961	−0.0410696	0.0390696
Ni	0.65	0.56 to 0.74	0.51	0.41 to 0.61	0.14	0.043	0.004486	0.2755139
Pb	1.59	1.32 to 1.86	1.33	1.02 to 1.64	0.26	0.213	−0.1492202	0.6692202
Sr	48	43.66 to 52.34	50.7	45.79 to 55.61	−2.700001	0.418	−9.248474	3.848473
Ti	0.27	0.24 to 0.3	0.23	0.2 to 0.26	0.04	0.046	0.0006893	0.0793107
U	0.13	0.11 to 0.15	0.18	0.16 to 0.2	−0.05	0.001	−0.0790813	−0.0209187
V	0.453	0.39 to0.51	0.35	0.28 to 0.42	0.103	0.03	0.0102138	0.1957863
W	0.03	0.02 to0.04	0.04	0.03 to 0.05	−0.01	0.026	−0.0188125	−0.0011875
Zn	296.93	268.87 to324.99	262.18	230.41 to 293.95	34.75	0.108	−7.639446	77.13945

*Al, aluminium; Fe, iron; Mg, magnesium; Mn, manganese; Ba, barium; As, arsenic; Cd, cadmium; Co, cobalt; Cr, chromium; Cs, cesium; Cu, copper; Hg, mercury; Ni, nickel; Pb, lead; Sr, strontium; Ti, titanium; U, uranium; V, vanadium; W, tungsten; Zn, zinc.

heavy metal weapons related contamination in Gaza since the first aerial attacks in 2004. Military attacks and restrictions on people's movement have become a prominent structural factor in the past 10 years. All participants in this study were present and residentially stable during three military operations in 6 years (Cast lead in 2008–2009, Pillar of cinder in 2012 and Defensive edge in 2014) and were likely exposed during that time and continuously thereafter to heavy metal war remnants that were environmentally stable. Even so, as the results highlight, this study was able to identify the contribution of heavy metals from the military attacks in 2014, establishing a significantly higher metal load in the hair of the women proximally exposed to these attacks. The composite background of war related heavy metal contaminants in the entire cross sectional convenience sample reflects the local history of attacks and had no bearing on the conclusions when we compared women exposed to those not exposed in 2014.

A general limitation of this type of study is that the knowledge about the effects of in-body interactions resulting from intake of more than one heavy metal is limited. It is difficult to anticipate the extent of the long term risk for human health and, in particular, for future pregnancies or infant development. Although we reported preliminary findings about incidence of birth defects and prematurity outcomes for the whole cross sectional convenience sample, this study was not designed to identify potential correlations between negative phenotypes in the newborns and heavy metal load. The size of this sample, while adequate to identify the correlation between levels of heavy metals with environmental exposures, is not large enough to generate accurate values for the incidence of negative birth outcomes, which have relatively low frequency in the population, or to establish the association of a high load of heavy metals with those outcomes.

Strengths of the study

The use of a questionnaire specifically designed to include local issues and administered via face to face interviews with women by their midwives allowed for the evaluation of the potential impact on the load in heavy metals of women's habits and exposures to sources of potential contamination other than military attacks. The questionnaire confirmed the rarity of other habits that could potentially lead to heavy metal exposure and to quantify as very low the geographical nearness to common anthropogenic sources of heavy metals in Gaza. The survey thus helped to verify and exclude a role for many potential confounders in the mothers' heavy metal load. A further strength of the study was the inclusion, as an internal control, of the testing of the concentration of microelements and metals not associated with weaponry. These did not differ in concentrations from the RHS reference, for both the exposed and not exposed groups.

This is the first investigation involving a sample with a relatively large number of participants, enlisted without

Table 3b Comparison between mothers of metal load between subgroups according to their ‘proximal exposure’. The metal load in mothers of different subgroups were compared with each other. Analysis was by multiple quantile regression on median values as linear function of the independent variable, ‘proximal exposure’. For ease in reading the data, the colour yellow indicates that the group in the column on the left in each panel has significantly higher load (p<0.05) than the one in the column on the right in the same panel. If vice versa, the line is enhanced in green colour. Panel C compares exposure subgroups 1+2 with 3; panel D compares exposure subgroups 1 with 2

Mother

C

Metal	Median exposures 1+2	95% CI	Median exposure3	95% CI	Difference	p>|t|	95% CI - INF	95% CI -SUP
Al	5.98	5.52 to 6.44	5.17	4.49 to 5.85	0.8099999	0.054	−0.0130119	1.633012
Fe	14.47	13.57 to 15.37	14.76	13.43 to16.09	−0.29	0.723	−1.894419	1.314419
Mg	533	495.29 to 570.71	436	380.61 to 491.39	97	0.005	29.98938	164.0106
Mn	0.8	0.73 to 0.87	0.58	0.47 to 0.69	0.22	0.001	0.0871368	0.3528633
Ba	4.76	4.03– to 5.49	3.79	2.71 to4.87	0.9700003	0.145	−0.3356257	2.275626
As	0.075	0.07 to 0.08	0.059	0.05 to0.07	0.016	0.011	0.0036835	0.0283165
Cd	0.0462	0.04 to 0.05	0.0429	0.03 to 0.05	0.0033	0.547	−0.0074508	0.0140508
Co	0.05	0.04 to 0.06	0.04	0.03 to0.05	0.01	0.09	−0.0015647	0.0215647
Cr	0.69	0.61 to0.77	0.58	0.46 to 0.7	0.11	0.134	−0.0340439	0.254044
Cu	12.7	11.91 to 13.49	12.8	11.64 to 13.96	−0.1000004	0.888	−1.499971	1.299971
Hg	0.186	0.16 to 0.21	0.198	0.16 to 0.23	−0.012	0.583	−0.0549375	0.0309375
Ni	0.65	0.57 to 0.73	0.46	0.34 to0.58	0.19	0.008	0.049235	0.330765
Pb	1.52	1.27 to 1.77	1.43	1.07 to1.79	0.09	0.685	−0.3461096	0.5261097
Sr	50.2	46.09 to 54.31	45.4	39.36 to51.44	4.799999	0.197	−2.504407	12.10441
Ti	0.27	0.25 to 0.29	0.22	0.19 to 0.25	0.05	0.014	0.0102301	0.0897699
U	0.141	0.12 to 0.16	0.177	0.15 to0.2	−0.036	0.027	−0.0678036	−0.0041964
V	0.454	0.4 to0.51	0.291	0.21 to0.37	0.163	0.001	0.0699174	0.2560826
W	0.04	0.03 to0.05	0.03	0.02 to0.04	0.01	0.058	−0.0003437	0.0203437
Zn	296.35	270.3 to 322.4	250.72	212.45 to288.99	45.63	0.053	−0.6644016	91.92441

D

Metal	Median exposure 1	95% CI	Median exposure 2	95% CI	Difference	p>|t|	95% CI - INF	95% CI -SUP
Al	6.1	5.538 to 6.662	5.76	4.551– to 6.969	0.3399997	0.616	−0.993446	1.673445
Fe	14.26	13.371 to15.149	15.91	13.998 to 17.822	−1.65	0.125	−3.758656	0.4586567
Mg	518	475.411–560.589	572	480.429 to663.571	−54	0.294	−154.9908	46.99076
Mn	0.77	0.683–0.857	0.89	0.703 to1.077	−0.12	0.253	−0.3260072	0.0860071
Ba	5.45	4.585–6.315	3.4	1.54 to 5.26	2.05	0.05	−0.0008681	4.100868
As	0.077	0.069–0.085	0.066	0.049 to 0.083	0.011	0.257	−0.0080663	0.0300663

Continued

Table 3b Continued

Cd	0.0466	0.04–0.053	0.0401	0.026 to 0.054	0.0065	0.418	−0.0092689	0.0222689
Co	0.05	0.042–0.058	0.05	0.033 to 0.067	0	1	−0.0191217	0.0191217
Cr	0.67	0.577–0.763	0.96	0.759 to 1.161	−0.29	0.01	−0.5112491	−0.0687508
Cu	12.7	11.873–13.527	11.9	10.123– to 13.677	0.8000002	0.423	−1.160014	2.760014
Hg	0.188	0.162–0.214	0.167	0.111 to 0.223	0.021	0.502	−0.0404448	0.0824448
Ni	0.65	0.549–0.751	0.72	0.504 to 0.936	−0.0700001	0.564	−0.3083581	0.168358
Pb	1.59	1.328–1.852	1.18	0.616 to 1.744	0.4100001	0.196	−0.2123387	1.032339
Sr	48	44.217–51.783	64.7	56.566 to 72.834	−16.7	0	−25.67073	−7.729264
Ti	0.27	0.243–0.297	0.25	0.192 to 0.308	0.02	0.54	−0.0441475	0.0841475
U	0.13	0.114–0.146	0.184	0.15 to 0.218	−0.054	0.005	−0.0916994	−0.0163006
V	0.453	0.395–0.511	0.519	0.395 to 0.643	−0.066	0.343	−0.2028334	0.0708334
W	0.03	0.016–0.044	0.11	0.079 to 0.141	−0.08	0	−0.1136928	−0.0463072
Zn	296.93	264.64–329.22	292.94	223.512 to 362.368	3.98999	0.918	−72.57932	80.5593

*Al, aluminium; Fe, iron; Mg, magnesium; Mn, manganese; Ba, barium; As, arsenic; Cd, cadmium; Co, cobalt; Cr, chromium; Cs, cesium; Cu, copper; Hg, mercury; Ni, nickel; Pb, lead; Sr, strontium; Ti, titanium; U, uranium; V, vanadium; W, tungsten; Zn, zinc.

exclusions, and which also includes newborn babies, where the load of 23 heavy metals was measured in participants' hair. The size of the cross sectional convenience sample allows subgroups to be used according to exposure to environmental factors, where even the subgroups were of suitable sizes for statistical analyses of the differences in median concentrations of contaminants. In addition, this is probably one of the first studies where women's recollections, in this case regarding their exposure to military attacks, was verified objectively by photographic documentation.

Interpretation

Heavy metal contamination as a hidden legacy of military attacks in 2014

The contamination by heavy metals associated with the exposure to recent military attacks is a hidden factor that has, until now, never been fully documented, even though it constitutes a risk for the health of the population. The frequency of women's exposure to the attacks in 2014 in a home setting was very high, about 70%, demonstrating the local's saying that there was 'no place to hide' for the population of Gaza at that time. The women exposed to attacks had significantly higher loads of heavy metals than women not exposed. As only about a quarter of women were primipara, three-quarters of the women had children who were similarly exposed to the military attacks. The extent of the attacks on civilians in 2014 was thus likely to have produced heavy metal contamination in a wide sector of the population.

The fact that the highest contaminant loads was found in the women exposed to attacks were in those not exposed involved various toxicants, teratogens and carcinogens (Ba, Al, V, Sr, Cr, W and As) , could not be foreseen a priori and illustrates the complexity of the contamination. Yet, this finding is compatible with the reports by various sources[25 27] about the use of many different types of ammunitions in this military operation.

We excluded some relevant sources as potential contributors to the heavy metal load detected in the cross sectional convenience sample. Chemicals used in agriculture and in the household did not impact on the metal loads when the entire sample was compared with references, or in proximally exposed women versus those not exposed. All other known factors considered are unlikely to be confounding. This is consistent with the known limited other anthropogenic sources of heavy metals in Gaza (like refineries and metal and chemical industries) and with the reduction in gasoline consumption for all uses, which was severely restricted due to the economic blockade in place since late 2012. Exposure to the 2014 attacks was the only factor that we could detect as contributing to the personal contamination of the participants by heavy metals.

Table 3c Comparison between newborns of metal load between subgroups according to the mothers ‘proximal exposure’. The metal load in newborns of different subgroups were compared with each other. Analysis was by multiple quantile regression on median values as linear function of the independent variable, ‘proximal exposure’. For ease in reading the data, the colour yellow indicates that the group in the column on the left in each panel has significantly higher load (p<0.05) than the one in the column on the right in the same panel. If vice versa, the line is enhanced in green colour. Panel A compares exposure subgroups 1 with 3; panel B compares exposure subgroups 1 with 2+3

Newborn

A

Metal	Median exposure 1	95% CI	Median exposure 3	95% CI	Difference	p>|t|	95% CI - INF	95% CI -SUP
Al	4.55	3.85 to5.25	5.71	4.79 to6.63	−1.16	0.049	−2.31712	−0.0028796
Fe	26.83	23.32 to 30.34	31.82	27.2 to36.44	−4.99	0.092	−10.78903	0.8090262
Mg	153	145.02 to 160.98	157	146.5 to167.5	-4	0.551	−17.1852	9.185197
Mn	0.3	0.25 to 0.35	0.3	0.24 to0.36	0	**1**	−0.0769879	0.0769879
Ba	0.4	0.35 to 0.45	0.36	0.3 to0.42	0.04	0.326	−0.0400217	0.1200217
As	0.011	0.01 to 0.01	0.011	0.01 to0.01	0	**1**	**−0.0019135**	**0.001913** **−0.0019135** **0.0019135** **5**
Cd	0.0056	0 to 0.01	0.0053	0 to 0.01	0.0003	0.737	**−0.0014518**	0.0020518
Co	0.02		0.02		0			
Cr	0.12	0.1 to0.14	0.13	0.1 to 0.16	−0.01	0.558	−0.0435074	0.0235074
Cu	7.31	7.02 to 7.6	7.87	7.49 to 8.25	−0.5599999	0.023	−1.042013	−0.0779871
Hg	0.0618	0.05 to 0.07	0.0544	0.04 to0.06	0.0074	0.258	−0.0054336	0.0202336
Ni	0.19	0.16 to 0.22	0.18	0.14 to 0.22	0.01	0.691	−0.0393955	0.0593955
Pb	0.2	0.17 to 0.23	0.22	0.17 to0.27	−0.02	0.499	−0.0780727	0.0380728
Sr	2.82	2.61 to 3.03	3.05	2.78 to3.32	−0.23	0.185	−0.5706677	0.1106676
Ti	0.24	0.2 to 0.28	0.25	0.19 to0.31	−0.01	0.78	−0.080361	0.060361
U	0.0014	0 to 0	0.0014	0 to0	0	1	−0.00055	0.00055
V	0.01	0.01 to 0.01	0.012	0.01 to0.01	−0.002	0.189	−0.0049906	0.0009906
W	0.04	0.03 to 0.05	0.04	0.03 to 0.05	0	1	−0.0115052	0.0115052
Zn	201.73	194.33 to 209.13	205.68	195.92 to 215.44	−3.949997	0.526	−16.19486	8.294866

B

Metal	Median exposure 1	95% CI	Median exposures 2+3	95% CI	Difference	p>|t|	95% CI - INF	95% CI -SUP
Al	4.55	3.81 to 5.29	5.98	5.14 to 6.82	−1.43	0.012	−2.549591	−0.3104087
Fe	26.83	23.01 to 30.65	33.11	28.83 to 37.39	−6.280001	0.032	−12.01936	−0.54064
Mg	153	144.43 to 161.57	165	155.39 to 174.61	−12	0.068	−24.87731	0.8773066

Continued

Table 3c Continued

Mn	0.3	0.24 to 0.36	0.35	0.29 to 0.41	–0.05	0.242	–0.1338956	0.0338956
Ba	0.4	0.34 to 0.46	0.43	0.37 to0.49	**–0.03**	0.494	–0.116016	0.056016
As	0.011	0.01 to 0.012	0.012	0.01 to0.014	**–0.001**	0.356	–0.0031258	0.0011258
Cd	0.0056	0.004 to 0.007	0.0065	0.005 to 0.008	**–0.0009**	0.337	–0.0027383	0.0009383
Co	0.02		0.02		**0**			
Cr	0.12	0.1 to 0.14	0.14	0.11 to 0.17	–0.02	0.247	–0.0539088	0.0139088
Cu	7.31	7.01 to 7.61	7.97	7.63 to 8.31	–0.6599998	0.004	–1.109277	–0.2107228
Hg	0.0618	0.05 to 0.07	0.052	0.04 to 0.06	0.0098	0.105	–0.002061	0.021661
Ni	0.19	0.16 to 0.22	0.21	0.17 to0.25	–0.02	0.444	–0.0712762	0.0312762
Pb	0.2	0.16 to 0.24	0.26	0.22 to0.3	–0.06	0.03	–0.1143081	–0.0056919
Sr	2.82	2.61 to 3.03	3.33	3.1 to3.56	–0.51	0.001	–0.8236846	–0.1963154
Ti	0.24	0.19 to 0.29	0.29	0.24– to 0.34	–0.05	0.156	–0.1190668	0.0190668
U	0.0014	0.001 to 0.002	0.0019	0.001 to0.002	–0.0005	0.067	–0.0010348	0.0000348
V	0.01	0.008 to 0.012	0.013	0.011 to 0.015	–0.003	0.037	–0.0058153	–0.0001847
W	0.04	0.03 to 0.05	0.05	0.04 to 0.06	–0.01	0.21	–0.0256367	0.0056367
Zn	201.73	194.37 to 209.09	210.16	201.89 to218.43	–8.430008	0.135	–19.50161	2.641593

*Al, aluminium; Fe, iron; Mg, magnesium; Mn, manganese; Ba, barium; As, arsenic; Cd, cadmium; Co, cobalt; Cr, chromium; Cs, cesium; Cu, copper; Hg, mercury; Ni, nickel; Pb, lead; Sr, strontium; Ti, titanium; U, uranium; V, vanadium; W, tungsten; Zn, zinc.

Table 3d Comparison between newborns of metal load between subgroups according to the mothers ‘proximal exposure’. The metal load in newborns of different subgroups were compared with each other. Analysis was by multiple quantile regression on median values as linear function of the independent variable, ‘proximal exposure’. For ease in reading the data, the colour yellow indicates that the group in the column on the left in each panel has significantly higher load ($p<0.05$) than the one in the column on the right in the same panel. If vice versa, the line is enhanced in green colour. Panel C compares exposure subgroups 1+2 with 3; panel D compares exposure subgroups 1 with 2

Newborn

C

Metal	**Median exposures 1+2**	**95% CI**	**Median exposure 3**	**95% CI**	**Difference**	**p>|t|**	**95% CI - INF**	**95% CI -SUP**
Al	4.98	4.3 to 5.66	5.71	4.72 to6.7	−0.73	0.233	−1.929914	0.4699142
Fe	28.53	25.41 to 31.65	31.82	27.29to-36.35	−3.289999	0.241	−8.794128	2.21413
Mg	160	152.59 to 167.41	157	146.23 to 167.77	3	0.652	−10.07445	16.07445
Mn	0.33	0.28 to 0.38	0.3	0.23 to0.37	0.03	0.478	−0.0530647	0.1130647
Ba	0.43	0.38 to0.48	0.36	0.29 to0.43	0.07	0.108	−0.0153842	0.1553842
As	0.012	0.011 to0.013	0.011	0.009 to0.013	0.001	0.344	−0.0010762	0.0030762
Cd	0.0061	0.005 to 0.007	0.0053	0.004 to 0.007	0.0008	0.398	−0.0010599	0.0026599
Co	0.02		0.02		**0**			
Cr	0.12	0.1 to 0.14	0.13	0.1 to 0.16	**−0.01**	0.601	−0.0475405	0.0275405
Cu	7.64	7.37 to 7.91	7.87	7.48 to 8.26	−0.23	0.339	−0.7023612	0.2423612
Hg	0.0592	0.05 to 0.07	0.0544	0.04 to 0.06	0.0048	0.46	−0.0079632	0.0175632
Ni	0.2	0.17 to 0.23	0.18	0.13 to 0.23	0.02	0.492	−0.0371107	0.0771107
Pb	0.23	0.2 to 0.26	0.22	0.17 to0.27	0.01	0.736	−0.0481337	0.0681337
Sr	2.96	2.76 to 3.16	3.05	2.75 to 3.35	−0.0899999	0.623	−0.4492506	0.2692508
Ti	0.26	0.22 to 0.3	0.25	0.19 to 0.31	0.01	0.784	−0.061673	0.081673
U	0.0017	0.001 to 0.002	0.0014	0.001 to 0.002	**0.0003**	0.277	**−0.0002415**	**0.0008415**
V	0.011	0.009 to 0.013	0.012	0.01 to 0.014	**−0.001**	0.486	**−0.0038153**	**0.0018153**
W	0.05	0.04 to 0.06	0.04	0.03 to0.05	**0.01**	0.169	**−0.0042687**	**0.0242687**
Zn	203.48	196.77 to 210.19	205.68	195.92 to215.44	**−2.199997**	0.715	**−14.04812**	**9.648124**

D

Metal	**Median exposure 1**	**95% CI**	**Median exposure 2**	**95% CI**	**Difference**	**p>|t|**	**95% CI - INF**	**95% CI -SUP**
Al	4.55	3.892 to 5.208	6.99	5.561 to8.419	−2.44	0.002	−4.012933	−0.867066
Fe	26.83	23.489 to30.171	36.64	29.457 to 43.824	−9.809999	0.015	−17.73244	−1.887563
Mg	153	145.207 to 160.793	188	171.334 to 204.666	−35	0	−53.39833	−16.60167
Mn	0.3	0.229 to 0.371	0.86	0.703 to 1.017	−0.56	0	−0.7319964	−0.3880036
Ba	0.4	0.342 to 0.458	0.73	0.606 to 0.854	−0.33	0	−0.4673186	−0.1926814

Continued

Table 3d Continued

As	0.011	0.009to 0.013	0.02	0.016 to 0.024	−0.009	0	−0.0128915	−0.0051085
Cd	0.0056	0.004 to 0.007	0.0104	0.008 to 0.013	−0.0048	0	−0.0074228	−0.0021772
Co	0.02		0.02		**0**			
Cr	0.12	0.096 to 0.144	0.19	0.135 to 0.245	−0.07	0.022	−0.1296617	−0.0103383
Cu	7.31	7.005 to 7.615	8.8	8.144 to9.456	−1.49	0	−2.213651	−0.7663499
Hg	0.0618	0.054 to 0.069	0.0468	0.03 to0.063	0.015	0.103	−0.003037	0.033037
Ni	0.19	0.157 to0.223	0.29	0.214 to0.366	−0.1	0.018	−0.1830964	−0.0169035
Pb	0.2	0.167 to 0.233	0.3	0.226 to0.374	−0.1	0.016	−0.1812501	−0.01875
Sr	2.82	2.631 to 3.009	3.78	3.374 to4.186	−0.96	0	−1.407472	−0.5125281
Ti	0.24	0.195 to 0.285	0.45	0.352 to0.548	−0.21	0	−0.3172189	−0.1027811
U	0.0014	0.001 to 0.002	0.0029	0.002 to0.004	−0.0015	0	−0.0022334	−0.0007666
V	0.01	0.008– to 0.012	0.014	0.01 to0.018	−0.004	0.044	−0.0078844	−0.0001156
W	0.04	0.007 to 0.073	0.15	0.079 to 0.221	−0.11	0.006	−0.1880415	−0.0319585
Zn	201.73	195.873 to 207.587	213.65	201.058 to 226.242	−11.92	0.092	−25.80754	1.967541

*Al, aluminium; Fe, iron; Mg, magnesium; Mn, manganese; Ba, barium; As, arsenic; Cd, cadmium; Co, cobalt; Cr, chromium; Cs, cesium; Cu, copper; Hg, mercury; Ni, nickel; Pb, lead; Sr, strontium; Ti, titanium; U, uranium; V, vanadium; W, tungsten; Zn, zinc.

Historical contamination by other war remnant heavy metals and their persistence in the environment

Besides the identification of a high load of heavy metals, which we specifically traced to exposure to the military attacks in 2014, we found that all the participants had levels significantly higher than controls from outside areas affected by war (RHS) of other war remnant heavy metals, such as U, Hg, Cd, Co, Fe, Ni, Pb, V, Mn, Cd and Co. Previous reports had shown their delivery in Gaza by weaponry; teratogens Hg and Cd and toxicants Pb and Fe were delivered by weapons in the 2008–2009 war.[6] A high load of Hg was reported in newborns of mothers exposed at that time to bombing and to attacks with white phosphorus ammunitions.[17–20] High loads of Al, Fe, Cd, Hg and U were detected in the hair of children tested 1 year after the 2008–2009 attacks (unpublished, Manduca).

The presence of concentrations higher than those found in the reference group (RHS) for heavy metals introduced previously by weaponry in Gaza in the entire cross sectional convenience sample of women that we have tested in 2015 confirms that these elements have persisted in the environment for years and suggests that the whole population may have been chronically intaking these metals.

Implications of chronic exposure to heavy metals and their in-body accumulation

Chronic exposure to heavy metals before the attacks in 2014 complicates the contribution of the attacks in 2014, and involves also diverse types of heavy metals. Yet, the heavy metals detected previously, as well those recently detected as deriving from the 2014 attacks, are known for their teratogenic, toxicant and carcinogenic properties. They are risk factors for non-communicable diseases and for reproductive health. On the one hand, the environmental stability of heavy metals makes it possible for their chronic intake from the environment by individuals. On the other hand, these metals, after intake into the body, are not excreted rapidly and accumulate in organs where they can continue to induce somatic epigenetic changes. If there is a threshold for their action , they can reach the critical concentrations capable of causing negative biological effects over time and can therefore affect health even at a time distant from that of intake, and pathological and phenotypic endpoints of their effects could be delayed.

A variety of negative effects in time affecting the physiology of individuals, as well as an increase in non-communicable diseases, were reported in association with heavy metal exposure. Unfortunately, very little knowledge is available to date on the kinetics of the deposition of each heavy metal in the body and of its release from each specific organ of deposition, and these unanswered questions require further investigation. Among the various potential long term negative effects associated with heavy metal intake, we here only discuss some of the concerns regarding reproductive health, for which some

Table 4 Comparison of metal load between mothers according to their use of house–agricultural chemicals. Subgroups are not users-subgroup 1 (n=352) or users subgroup 2 (109), of any of the chemicals listed in figure 3D . Analysis was by multiple quantile regression on median values as linear function of the independent variable, 'use of chemicals'. There was no significant difference for the load of all metal tested (p > 0,3) between the two groups

Metal	Subgroups	Median	es	t	p	Inf 95% CI	Sup 95% CI
Al	1–0	0.4099998	0.4472674	0.92	0.36	–0.4687552	1.288755
Fe	1–0	0.3400002	0.8071532	0.42	0.674	–1.24583	1.92583
Mg	1–0	–32	36.53437	–0.88	0.382	–103.7798	39.77981
Mn	1–0	0.07	0.0755919	0.93	0.355	–0.078517	0.2185169
Ba	1–0	0.0299997	0.6327794	0.05	0.962	–1.213234	1.273234
As	1–0	0.003	0.0067409	0.45	0.656	–0.010244	0.016244
Cd	1–0	–0.0029	0.0053168	–0.55	0.586	–0.013346	0.007546
Co	1–0	0	0.006578	0	1	–0.012924	0.012924
Cr	1–0	–0.02	0.0771729	–0.26	0.796	–0.1716231	0.131623
Cs	1–0	0					
Cu	1–0	0.1999998	0.6981627	0.29	0.775	–1.171694	1.571694
Hg	1–0	0.001	0.0219324	0.05	0.964	–0.042091	0.044091
Mo	1–0	–0.003	0.0057415	–0.52	0.602	–0.0142804	0.0082804
Ni	1–0	–0.06	0.0769901	–0.78	0.436	–0.2112641	0.0912641
Pb	1–0	–0.0599999	0.2266566	–0.26	0.791	–0.5053166	0.3853167
Se	1–0	–0.0100001	0.0171442	–0.58	0.56	–0.0436837	0.0236836
Sn	1–0	–0.01	0.0159526	–0.63	0.531	–0.0413423	0.0213423
Sr	1–0	2.5	3.742336	0.67	0.504	–4.852641	9.852641
Ti	1–0	–0.01	0.0215455	–0.46	0.643	–0.0523308	0.0323308
U	1–0	0.009	0.0156546	0.57	0.566	–0.021757	0.039757
V	1–0	–0.019	0.0510704	–0.37	0.71	–0.1193391	0.0813391
W	1–0	0	0.004584	0	1	–0.0090062	0.0090062
Zn	1–0	–14.70999	23.91878	–0.61	0.539	–61.70368	32.2837

*Al, aluminium; Fe, iron; Mg, magnesium; Mn, manganese; Ba, barium; As, arsenic; Cd, cadmium; Co, cobalt; Cr, chromium; Cs, cesium; Cu, copper; Hg, mercury; Mo, molybdenum; Ni, nickel; Pb, lead; Se, selenium; Sn, tin; Sr, strontium; Ti, titanium; U, uranium; V, vanadium; W, tungsten; Zn, zinc.

information in humans is available, as well as the role of teratogens of some of the heavy metal contaminants.

Exposure to attacks, heavy metal load and long term implications for reproductive health

We have mentioned the limits of this study in investigating the association of the metal load with phenotypes at birth. The present study is a first step in this direction. Nonetheless, the finding of an increase in birth defects and preterm births, compared with the incidence registered in 2011, is a concern.[21] We can anticipate that our data on a widercross sectional convenience sample would register significant increases in birth defects and preterm births by the year 2016 (Manduca *et al*, submitted 2016). In other post-war settings, the association between exposure to attacks and negative reproductive outcomes was reported.[18] In Gaza, by retrospective pedigree analysis,[20] an increase in birth defects was reported starting in 2005, after the newest air delivered weapons were first used. Between 2006 and 2010, i.e. before and after the Cast lead operation in 2009, there was a significant increase in birth defect in infants,[19] a rise which was continuing in 2011 (Manduca, unpublished). In Gaza was reported in 2011 association between the exposure to attacks and the contaminant load in newborn hair for specific teratogens, if the infant was born with a birth defect, or toxicants, if the infant was born preterm.[22] There is thus some evidence of the potential negative impact on the outcomes of pregnancies due to the intake of heavy metals during wars.

There was also limited previous evidence that most of the heavy metals pass through the placental barrier, as we here documente, and accumulate in the hair during fetal life. However, the critical levels of heavy metals capable of negatively impacting on the human embryo and fetus are unknown, and little is known about the kinetics and modalities of trans-placental transfer of each individual heavy metal over time.

We have reported that newborn babies in this cross sectional convenience sample have lower heavy metal loads than mothers, but our present knowledge does not allow for a conclusion of whether this is reassuring for their future health as infants. Delayed effects were reported for in utero exposure to attacks among children as increased rates of chronic illnesses, developmental problems and growth impairments.[7–10 12–16] Our data on newborn contamination are only an initial contribution to the needed research to investigate whether a high maternal load of weapons related metals and in utero exposure of the baby can predict physical, cognitive, emotional and psychological development in the infant. We are presently addressing this issue with a longitudinal assessment.

Other long term exposures to heavy metals that could harm the infant's development may occur because of the transmission of heavy metals from the mother through breastfeeding.

A high load of some heavy metals can interfere with the mother's future capability to bring a pregnancy to term, resulting in premature deliveries or negative effects on their next babies' health.[11 29] Mobilisation during pregnancy of metal previously accumulated in the mother's body is likely to occur in pregnancies remote in time from their intake, and the return of stored heavy metals into the lymphatic and vascular circulation may have delayed effects on reproductive health.[21 22] There is evidence that different heavy metals accumulate preferentially in different compartments of the body (eg, bone for lead, strontium and uranium; brain for mercury, cadmium and aluminium; kidney for cadmium, mercury, chrome, lead and plutonium), and that from these organs, the metals can be mobilised during subsequent pregnancies, via organ and tissue remodelling, and the development of the placenta, but the extent and details of these mobilisations are largely unknown.

Generalising the meaning of the study

The results of this study illustrate that in Gaza, a specific high load of heavy metals is associated for all the women in the cross sectional convenience sample with the exposure to military attacks in 2014, and widespread contamination for many heavy metals was associated with the use of weaponry in previous attacks. These evidences support the possibility of immediate and long term risks for health posed by weapons associated heavy metals and war remnants. They suggest that the risks posed by the war remnants are diffuse, may not be limited to reproductive health and may also affect the frequency of pathologies such as cancers, male sterility, immunity and endocrine disorders, thus interesting all sexes and ages, as the insurgence of these pathologies can be influenced by heavy metal exposure and is noticeable that they are reported by medical sources, on the rise in Gaza.[8–11]

The contamination documented in the cross sectional convenience sample by potential effectors of non-communicable diseases suggests new investigative lines in studying their ethology.

The relevance of the local context needs to be underlined as the it was the first determinant that made our research possible. There are factors in the Gaza Strip that aided conducting human studies which would hardly be possible elsewhere: good medical structures, collaborative communities with stable composition and residences, and stagnating or restricted industrial production (although imposed by the siege and negative for the well-being of the people), independent documentation from international observers of timing of attacks and of kind of weapons used , and consulting help for environmental issues. The collaborative context also allowed the development of a questionnaire suitable for further surveillance of health.

To fully understand the implications for health of these findings we need future studies involving a variety of professional aptitudes. Research is needed on the fate of heavy metals in the human organism, particularly in relation to the release from the mother's organ during remodelling in pregnancies. Additionally, researchers should explore the mechanistic aspects of the molecular action of each heavy metal, and longitudinal studies can identify and verify the endpoints of diseases over time. Currently, knowledge of all of these matters is limited. Given that the weaponry used in many of the current military operations in other countries is often manufactured by the same firms as the weaponry used in Gaza, our observations may be relevant in designing studies in other settings.

CONCLUSIONS

The long term effects on health due to contamination by remnants of war containing heavy metals needs consideration in association with other long term effects of war on populations, including the trauma of war and war related economic and structural damage.

Surveillance at birth, bio-monitoring and the study of outcomes of maternal and newborn health must be maintained as stable programmes, as they provide the most sensitive first sentinels for studies of the sequelae of anthropogenic contamination and can provide alerts about increases in damaging health conditions. They also provide solid information intrinsic to prospective data collection. Surveillance at birth is relatively easy to implement, and its outcome informs the general risks for the population and helps tailor public health interventions and preventive procedures.

Retrospective and longitudinal investigations should be undertaken to investigate the effects of heavy metal contamination on non-communicable diseases

Further research on the long term health damage caused by exposure to heavy metals is needed. Additionally, plans for family counselling, prevention and remediation should be developed. These efforts require the support of the scientific community and the involvement of an array of professionals from different disciplines. Our studies provide a background for others to be implemented in other settings where, in similar fashion as in Gaza, general health may be threatened by hidden remnants of war in the present and for the next generations.

In summary, in Gaza, contamination by heavy metals that persist in the environment and their continuing accumulation in individuals are ongoing risk factors for a variety of health outcomes in the aftermath of war.

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Contributors Contributorship statement. PM developed the questionnaire used to collect the data, directed the analytical work and elaboration of the data with statisticians, wrote the manuscript, and prepared the figures and reference list. SYD directed the organised field work in three hospitals, and the follow-up objective assessment of damages, and contributed to the definition of the work and review of the manuscript. NMAA directed the organised field work in one hospital and contributed to the definition of the work and review of the manuscript. SRQ partecipated in the planning of the study and review of the manuscript. R-LP launched the idea of the study and participated in the planning of the work and first draft and review of the manuscript. All contributed authors had access to and revised the data.

Competing interests None declared.

Patient consent Yes.

Ethics approval The Palestinian Health Research Council and the Helsinki C'ommittee for Ethical Approval approved the study, and the Research Board of the Islamic University of Gaza, Palestinine, reviewed and accepted the research tools and procedures. The women provided written informed consent for their own and their newborns' participation.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement Extra data can be accessed via the Dryad data repository at http://datadryad.org/with the doi:10.5061/dryad.kr846.

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