

# Synchronic and Diachronic Investigation of the Long-Term Effects on Reproductive Health of Heavy Metals, Environmentally Stable Military Remnants in Gaza, Palestine: A Summary

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**Abstract:** Here is reported research “on the other side of weapons”, that of the victims, aiming to diffuse knowledge of the long-term damages to health by heavy metals in weaponry, invisible and stable war remnants in the XXI century wars. The work reported is exemplary in identifying at each time point (synchronic approach) and along 13 years (diachronic approach) the source of heavy metal contaminants in weaponry, their chronic uptake by humans and proving association of exposure to attacks and metal contamination with reproductive damage in the war setting of Gaza Palestine. Many heavy metals found in weaponry are toxicants, fetotoxic and carcinogens, are spread indiscriminately by ammunitions, are stable in the environment, suggesting that their use in attacks on civilian areas falls under more than one prohibition by international law. To date, we are not aware of other studies of surveillance of reproductive health in any war area on a wide random cohort, nor of this being accompanied by systematic parallel investigation of human contamination by heavy metals delivered by weapons, white phosphorus shells, and in wounds by not-fragmenting ammunitions. The data altogether, allow comparison among time points (diachronic view); this view allowed to understand the entity of the long-term effects of metal contamination of mothers on birth outcomes, the persistence of these effects vis a vis the environmental contamination, to single out and confirm which of the many metal elements found at high levels in post-war area is affecting negatively the outcomes at birth, and to describe long-term impact of recent war events on health, before and after displacement of war remnants. It documents that one of the tolls by war-remnant heavy metals contamination is increase of deaths in the perinatal age, “invisible war victims”.

## 1 INTRODUCTION

These investigations focused on the role of heavy metals, fetotoxic and carcinogenic or toxic for mammals, and “invisible stable weapons remnants” of war, and on their role as effectors of negative reproductive health outcomes.

Heavy metals, components of many weapons systems of this century, which Israel used on Gaza, do not disappear from the environment, and have the potential to cause, by various mechanisms, long-term health damages upon acute and chronic exposure and via accumulation in organs (Domingo, 1994; AIRC, 2020; ATSD, 2011; Rice, 2014; Amadi, 2017; Wai, 2018; Rahman, 2016; Cheng, 2012; Grandjean, 2105; Bommarito, 2017).

Military aggressions and wars draw an almost continuous line of fire along the last 23 years, from

Yugoslavia through Southwestern, Western and Central Asia, Middle East, and north Africa. Although the impact of stable war remnants is a concern in each of these places of war, there are only sporadic scientific reports about these stable chemicals, heavy metals delivered by weaponry, in association with negative outcomes of reproductive health of populations.

To investigate the changes in reproductive health associated to contamination of a population by stable effectors as heavy metals delivered by weaponry, poses many challenges of various nature.

Daunting ones are the lack of specific biomarkers of their biological effects, the scarce knowledge about the mechanism of action of heavy metals, and the complexity due to the compresence of several heavy metals in the war-remains. Much more work is necessary to tackle these aspects.

Some wars are ongoing, posing difficulties in access. Others have been very long, and even after the wars, there have been “intrinsic” factors hindering adequate design for systematic studies, e.g., the displacement of populations and/or the concomitance of other crisis also potentially impacting health, lack of previous birth registry to use as reference.

There was also decisive hindrance by “extrinsic” factors, local governments, or external occupiers, opposing to the documentation of long-term effects on reproductive health potentially due to the weaponry used and to their remnants, because this documentation could imply responsibilities for having used these weapons in wars waged extensively on the civilian populations. Thus, local, and occupying authorities took unhelpful, or at time threatening, postures against the research, even when collaboration was sought by local professionals; international health bodies, when intervened, often did not publish the results in scientific journals with review.

In Gaza, aside minor events, the research work was accepted and facilitated by the local authorities, the UN bodies in the field, and by highly collaborative professionals. What is presented here is the result of a collective effort.

In Gaza the “intrinsic” conditions allowed to adopt a satisfactory scientific design; paradoxically, the inhuman siege contributed to make easier some of the aspects of the research, since it forced people to residential stability, thus defining the length of post-war chronic exposures to war remains and allowed to trace the chronology of the removal of ruins and war remnants.

Positive “extrinsic and intrinsic” conditions in Gaza allowed to persevere in the investigations for 13 years, for what is an unprecedented span of time in any war area, although with interruptions due to the 3 wars waged on Gaza meanwhile (2009, 2012, 2014). Nonetheless, the recurring attacks with varied set of weaponry posed an extra challenge to the interpretation of data.

Anyhow, it was possible to acquire reiterate extensive synchronic information through surveys at birth and parallel analytical data of metal load in women and newborns, and to include verified recall of exposures to potential environmental sources of heavy metals; repeat of the surveys and assessments in time, having developed and used the same standard methodology for acquiring data along the years, allowed to compare diachronically the sets of yearly data.

The investigation in Gaza covered the span of the years 2006- 2019. It started documenting the delivery

by weaponry of heavy metals, and its assumption by the population. It involved studies of human contamination by heavy metals in random cohorts. One of them was of 95 children; 5 were cohorts of women delivering a baby, for a total of 14.000 women, including some exposed at different and multiple times to major military assaults by the Israeli army. The survey of the outcomes of birth involved about 13.500 women, in 4 cohorts.

The studies also collected, through collaboration with UN and local environmental and agricultural authorities, analytical and historic details of the environment and of usage of chemical in civil life, obtaining a body of circumstantial information, including that about the localization of military attacks which confirmed women’s recall of exposure to these attacks. Together, this extended consultancy surrogated the interpretation of association of heavy metals in weapons remnants as effectors of reproductive health and helped to understand the timing and circumstances that caused the diffusion of these effectors in the environment.

The research developed stepwise; each step motivated by the results of the previous one and incorporated the novel questions that these posed; it resulted in obtaining eventually a picture of the environmental contaminants delivered by weapons, of the pattern of their assumption by civilians under acute and under chronic exposures and of the correlation of the assumption of heavy metals by women with their reproductive outcome.

Rare sporadic reports, and our own unpublished data from other war areas suggested decrease in reproductive and whole health in people residing in locations militarily attacked, and, in some cases, reported human and environmental contamination by heavy metals.

A word will be spent on the potential use for the information presented here.

## 2 METHODOLOGIES

Multiple sources of information were used, various scientific tools and different methodologies appropriate to cover each sector of the investigations and these were published (Skaik, 2010; Abed, 2014; Naim, 2012; Manduca, 2011, 2013, 2014, 2019; Baraquoni, 2020; Vänskä, 2019).

The research involved field work, environmental assessments, and hospital-based work with local professionals as partners and consultants and analytical measures were done abroad certified labs, the same since 2011.

Protocols were prepared for each step of the work: adequate collection for the analysis of inert and biological samples, clinical and environmental data recording and preservation of biological samples for analytical studies.

Inert samples from bombed sites or ammunitions, were used to investigate the presence of heavy metals in weapons used in Gaza. Hair was collected of 4cm length at the nape for adults. The appropriacy for analytical studies on formalin preserved biological samples was also tested.

The amount of 23 heavy metals in inert materials, hair and in biopsies of the wounds was determined by Inductively Coupled Plasma Mass Spectroscopy (ICP-MS) in 2 certified laboratories in Italy and in Canada. All hair samples of women and babies were analyzed in the same laboratory which legitimizes comparisons. In all the analysis appropriate controls were utilized. E.g. for inert samples, the soil from outside the crater zone; for biopsies, layers of the tissue at a distance from the wound from the same individual; for hair, adult controls were from individuals from countries outside the war area and for newborns the hair of normal Gaza's babies.

Detailed protocols for collection of participants consensus and hair samples, questionnaires for registration of data at birth from mothers included questions on mother's historical health records, parity, prenatal prevention care and provider, nutrition, medication and habits, marriage with first- and second-degree relatives, but also health records for the other children of the couple, and for the parents' extended family, data on child sex, living parameters, clinical diagnosis, singlet or twin, type of delivery. The questions on exposures to possible toxicants/teratogens in civil life (8), on military events exposure (15 or more), about the state of the dwelling and rubble reuse after wars (4) were updated after each new war to account for the changes in the environment.

### 3 RESULTS

#### 3.1 Chronology of Military Attacks

The temporal context of the major attacks in Gaza is shown in Table I with the extent of damages since 2008.

Table 1: Chronology of the major military attacks on Gaza before 2021, number of victims/damages.

	Dec 2008- Jan 09	Nov-12	July -Aug 2014
Duration (days)	22	8	55
Palestinians killed	1409	174	2251
children killed	348	32	551
injured	5380	1000	11231
Houses damaged/destroye	14000	2174	18000

The attacks reported here followed a shorter but intense one in 2006, when were used for the first time weapons that caused wounds without fragments strikingly like those reported at the same time in the contemporary war to Lebanon. Call for help to understand the strange wounds that were presented with in these attacks, issued by doctors in these two countries to professionals abroad, and their reports of unexpected prognosis after care for these previously unseen wounds, together with the published information of the development by US firms of metal-augmented weaponry, and the acknowledgement by Israel of "field testing" novel weaponry, triggered our research "on the other side" of weapons.

#### 3.2 Heavy Metal Remnants Delivered by Weapons in the Environment and in Wounds

Craters and WP ammunition were tested for the kind and load of heavy metals and were shown to delivery fetotoxic and carcinogen metals (Table II).

Table 2: Qualitative summary of content in heavy metals, among the 23 tested, which were found in fivefold or more amounts compared to controls. Al - aluminum, Hg - mercury, W - tungsten, Mo - molybdenum. WP = white phosphorus. Yes >5 fold than control.

	Al	Hg	W	Mo	fetotoxic
craters	yes	yes	yes	yes	Fetotoxic-carcinogen
WPshell	yes	yes	yes	yes	

The craters tested were produced in 2006 and 2009 by heavy bombs that made wide and deep holes in land. In 2009, 3500 WP shells, each spreading its content for a radius of 300m, were used on Gaza, potentially covering with their content 1/9 of the surface of the Gaza strip.

Biopsies at the site of wounds caused by weapons without fragments, including White phosphorus burns, were collected, and tested for their metal

content, as proof of fact that the weapons that had produced them delivered heavy metals.

Tissue from 15 victims was analyzed. Each wound was clinically classified by surgeons. Wounds within the same group of clinical classification had similar content and quantity of metals, while wounds in clinically different groups had a different specific metal signature.



A-C amputees, D simple burn, E-F and I charred, G-H White phosphorus

Figure 1: Wounds from victims in 2006 and 2009 from which biopsies were analyzed by ICP/MS.

In Fig 1 is shown the kind of damage inflicted to the victims and the clinical classification of wounds, and in Table III the comparison of the load of heavy metals detected in the tissue from each clinically different kind of wounds.

Table 3: Qualitative summary of metal load in clinically different wounds and date of the wounding. Cd-cadmium; U- uranium; V-vanadium; Sr-strontium; Cu-copper; Ba-barium; Sn-tin. Yes highlighted in green > 5fold than control; yes highlighted in blue >2 fold than control.

Metal	Al	Hg	W	Mo	Cd
WP wound 2009	yes	yes	no	yes	no
Amputations 2006-09	yes	yes	no	no	yes
Carbonized 2009	yes	yes	no	no	no
burns 2009	no	yes	no	no	no
Metal	V	Sr	Cu	Ba	Sn
WP wound 2009	no	yes	yes	yes	yes
Amputations 2006-09	yes	yes	yes	yes	no
Carbonized 2009	yes	yes	yes	yes	no
burns 2009	no	no	no	no	no
Metal	Pb	Ni	B	Co	U
WP wound 2009	yes	yes	no	no	yes
Amputations 2006-09	yes	no	yes	yes	yes
Carbonized 2009	yes	yes	yes	no	no
burns 2009	yes	no	no	no	no

The data are proof of fact that weaponry without fragments each delivered heavy metals, and that the metal signature was specific for the different clinical damages inflicted.

### 3.3 Human Intake of Heavy Metals Delivered by Weapons

Testing the hair of 95 children for the load in 23 metals 8-9 months after the attacks in 2009, showed that 60% of them had higher load in the hair grown in the last 3-5 months for all the toxic metals reported in Tables II and III than control children living in 2 towns in Italy and 1 town in Israel, and of the standards load form other not war areas (not shown).

This finding implied that was ongoing human contamination by metals delivered by weaponry and signaled chronic intake by a wide segment of the population, alerting to the possibility that high level of contamination of humans might affect their health for a long time, and might negatively interfere with pregnancy, embryo, and fetal development.

### 3.4 Changes in the Prevalence of Major Structural Birth Defects Bridging War- Retrospective Approaches

Aware of the potential risks of heavy metal contamination for reproductive health, two retrospective approaches were used to assess if there had been changes in prevalence of major structural birth defects (BD) in the time bridging the 2009 war: analysis of data retrieved from registers of all pediatric hospitals in Gaza (Table IV), and reconstruction of BD incidence in the history of more than 40 families with a normal child born in 2011 (Fig.2).

From the records of the pediatric hospitals in Gaza was calculated the prevalence of major birth defects occurring at two time points, in 2006 and 2010, spanning the military attacks in 2009 (Table IV).

Table 4: Prevalence of BD among 0-2 years old children registered in all Pediatric hospitals of the Gaza strip in the first six months of 2006 and 2010.

First 6 months of year	2006	2010	p value
BD patients	274	331	
Total 0-2 year old patients	6920	5254	
BD (0 -2 years old)/1000	39.6	63	<0,001
Children born in the biennias	93.760	98.064	
Minimal estimated prevalence/1000	5,83	6,76	<0,001

Increase (p<0,001) in 0-2 years old patients with BD occurred spanning the attacks in 2009.

Collecting from parents the self-reported events of BD in their progeny and the date of birth of all their children, is possible to reconstruct the frequency of

BD in the progeny as they occurred in time (Figure 2).

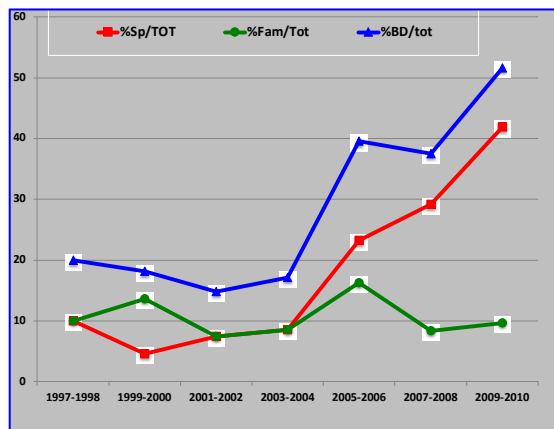


Figure 2: Increase in time (1997-2010) of the frequency (%) of major malformations in families with a normal newborn in 2011 and with a previous child with birth defect. Sp=sporadic, Fam=documented familiar. Cochran-Armitage trend test for Sporadic malformations  $p < 0.001$ , for familiar malformations  $p = 0.59$ .

The prevalence of BD increased in time between 1997 and 2010; those BD for which there was not documented familiarity contributed disproportionately to the overall rise, supporting the hypothesis that environmental effectors affected the incidence of BD and that these effectors were introduced between 2006 and 2010.

The two independent retrospective approaches showed the increase in prevalence of BD bridging the 2009 war. The two approaches concur to signal increase in BD after the major war in 2009.

The reconstruction approach sets the starting time of the increase to the first campaigns of airstrikes on Gaza; these started in late 2005 as soon as colonial settlers left the Gaza Strip;

### 3.5 Association between Mother's Exposure to Attacks, Progeny Outcome, and Metal Contamination in Newborn Hair

A survey at birth was conducted to establish if there was a correlation between the exposure of women to attacks and their probability to have a baby with BD, and if the BD babies had a higher load in heavy metals than normal babies. Survey at birth was implemented in Gaza in 2011. Data of a random cohort of almost 3000 delivering women were collected in sequence in one Maternity. In the registration questionnaire included questions about exposure of the mother to

potential negative effectors of health (habit to smoke tobacco or shisha, use of drugs, use of chemicals, nearness to/work in industrial and agricultural areas and exposure to previous military attacks) and historic residence of the couple.

In this cohort of women those that recalled being under bomb and/or WP attacks in 2009 had with significant higher frequency newborns with BD, compared with women not exposed to attacks ( $p < 0.001$ ) (Table V).

Table 5: Correlation of the mother exposure in 2009 to attacks, by kind of weaponry, with the prevalence (%) BD in their progeny born in 2011.

Exposure	total N	None		WP		Bombed		WP & Bombed	
		N	Prevalence (95% CI)	N	Prevalence (95% CI)	N	Prevalence (95% CI)	N	Prevalence (95% CI)
Normal	2,933	2,88	98.3(98-99)	49	1.7 (1-2)	N/A		N/A	
BD	44	19	43.1(29-58)	12	27.2 (14-40)	9	20.4 (9-32)	8	18.2 (6.8-29.6)
Overall	2977	2,9	97.5(97-98)	61	2.0 (2-3)	N/A		N/A	

Recall by mothers of their exposure to military attacks was verified, crossing the address of their residence with the place and kind of ammunition used in attacks, on the maps recording military attack, accessed by courtesy of the UN Mine Action Team.

The hair of newborns in the cohort was collected within 5 minutes from delivery, metal load was measured, and the results indicated passage of heavy metals in utero.

Comparison of the load of heavy metals in BD versus normal babies, showed significant higher amount of mercury ( $p < 0.003$ ), tin ( $p < 0.002$ ), and selenium ( $p < 0.004$ ) in BD newborns than in normal babies. Preterm babies, also tested, showed a different pattern of contamination than BD and normal newborns, having higher load in barium ( $p < 0.03$ ) and tin ( $p < 0.002$ ).

There was correlation between mother exposure to weapons, negative outcome of pregnancy, and higher load of heavy metals in BD or preterm newborns hair than in normal babies. The contaminants in highest load were specific: mercury and selenium for BD and barium for preterm.

The association of these specific metals in high load respectively in BD and preterm, is consistent with what is known respectively about the teratogenic effect of mercury, and the synergism in teratogenicity of high loads of selenium with mercury, and about the toxicant effect during pregnancy of barium.

The association: mother exposure to attacks-negative birth outcome-high load in specific heavy metals was found almost 2 years after the women were exposed to the attacks in 2009, implying long-

term effects of an event of acute contamination and/or effects due to long resilience in the environment where heavy metals war-remnants remained, and ongoing chronic contamination. It is compatible with the second possibility the fact that these women, in the large majority of cases (90%) continued to reside in the place where the attacks had occurred, and remains of weaponry remained in or near their housing.

### 3.6 Recent Exposure to Military Attacks Increased the Load of Heavy Metals Above a High Background in a Cohort of Women and Their Newborns

In early 2015, was assessed the extent of women contamination in relationship with recent exposure to weaponry of a cohort of 502 women, who were 1-3 months pregnant during the attacks in 2014. 70% of the women recalled exposure to the recent attacks on their housing; their recall was verified in 108 random cases, and damages to their housing was confirmed in 99% of the cases by photos.

Hair from the mothers and their newborns was tested for metal load, reflecting the last 4 months of accumulation in mother and the whole fetal life in the newborns. It was found positive correlation between proximity of the mothers to military attacks and a higher load of toxicants (Ba, Al, V, Sr, Cd and Cr), teratogen (Hg, W) and a carcinogen (As) compared to women not exposed to attacks (30% of the cohort). There was no difference for the concentration of microelements (Cu, Se, and Mo).

Trans-placental passage occurred for heavy metals from mothers to their newborns, the median metal load of the babies being much lower than the mothers' load.

Of relevance, the samples of hair from these 502 Gaza women had higher 95 percentile values of concentration compared with a standard control of hair from individuals the outside war area (Table VI) for heavy metals of relevance for health and identified as weapon remnants also from previous attacks, in 2009.

Table 6: 95percentile of the load (ppb) of 23 metals in the cohort of 502 mothers that delivered in 2015, compared to standard controls (in red). Highlighted in blue are the metals with values higher for women in Gaza than for the controls, column on the right indicate the p value for the comparison. Molybdenum, selenium, tin and titanium showed no significant difference from controls.

Metal	95°pct	95 CI		95°pct	comparison mother with ref
<b>2015 Mothers (N=502)</b>				<b>reference German</b>	<b>p value</b>
Al	16,91	13,88	21,68	<8	<0,05
Fe	40,16	35,25	52,28	1.6-17	<0,05
Mg	1260	1123,9	1457,9	20-130	<0,001
Mn	2,9	2,38	3,44	0,05-0,92	<0,05
Ba	29,69	24,04	49,18	<4,64	<0,05
As	0,24	0,21	0,28	<0,2	<0,05
Cd	0,24	0,2	0,3	<0,2	<0,05
Co	0,57	0,37	0,76	0,01-0,30	<0,05
Cr	2,93	2,43	3,29	0,02-0,21	<0,05
Cs	0	0	0	<0,01	not detected
Cu	40,73	33,6	52,24	10-41	=
Hg	1,62	1,16	4,84	<0,60	<0,05
Mo	0,26	0,21	0,32	0,03-1,00	=
Ni	2,76	2,23	3,56	<1,00	<0,05
Pb	6,5	6	7,35	<3,0	<0,05
Se	0,88	0,86	0,95	0,40-1,70	=
Sn	0,75	0,61	0,98	<0,70	=
Sr	136	122,39	160,26	0,65-6,90	<0,005
Ti	0,82	0,73	1	<1,50	-
U	0,53	0,46	0,68	<0,10	<0,05
V	1,4	1,26	1,56	0,01-0,20	<0,005
W	1,37	1,07	2,28	<0,02	<0,001
Zn	990,55	902,21	1202,9	150-272	<0,005

These data point to a high background of already existing contamination by weapon remnants and to chonical assumption, to which the recent attacks added quantitatively.

### 3.7 Birth Registry and Prevalence of Negative Outcomes at Birth, from 2011 to 2019

Comparison of birth surveys taken in different years was possible because the same methods, procedures, and randomness of the cohorts, was used. It showed that further increase in the incidence of birth defects and preterm babies occurred from 2011. The increase, between 2011 and 2016, bridging 2 wars in 2012 and 2014, was very significant; prevalence values did not change significantly after 2016.

Table 7: Comparison of the incidence of negative birth outcomes (%) in surveys in 2011, 2016 and 2018-2019. In each of these years respectively 2940, 6104, 4707 deliveries were registered in sequence. Preterm, born before 37 weeks of gestation age; BD, birth defect. N is the number of cases. Highlighted in blue, the p values of significant differences in incidence between years.

Prevalence of outcomes at birth in the years 2011, 2016 and 2018-2019.							
year		2011	2016	2018-19	p-Value	p-Value 2011 vs 2018-19	p-Value 2016 vs 2018-19
Preterm	N	45	482	360			
	%	1.1	7.9	7.6	<0.001	<0.001	0.509
BD	N	44	108	78			
	%	1.1	1.8	1.9	0.019	0.028	0.597

For BD the change in prevalence was not associated to increase in intermarriages, which instead decreased since 2011. The increase in BD between 2011 and 2016 was substantial in such short time, and so was the contribution of sporadic novel cases, deduced in the basis of the family history, also collected in the survey. The change of the prevalence in preterm is extremely relevant and compatible with being induced by chronic exposure to metal contaminants in the environment which likely accumulated during the two wars in 2012 and 2014).

### 3.8 Assessment of Exposures, Metal Load in Mothers in Relation with Outcome of Pregnancy, Years 2011-2019

In the 6-9 months after the attacks in 2014 the load of metals in mothers exposed to them was higher than in not exposed. Between 2015 and 2019 there were no major new military attacks on Gaza.

The two major military attacks in 2012 and 2014 were accompanied by extensive destruction of housing and infrastructures and, following these attacks, clearing of the debris and reconstruction had to wait years to be done, due to lack of machinery and cement imposed by the blockade by Israel and, since 2013, also by Egypt.

Cleaning up started in middle 2016, involved removal of the rubble of destroyed buildings and infrastructures and its reuse through pulverization of the debris in open air and disposing of the biggest chunks by or into the sea.

Before this time, the rubble remained largely in the proximity of hit buildings and infrastructures, in the roads and fields, available to be washed out and dispersed by flood rains and enter the (still) open sewage. In 2016, 34% of the cohort of mothers in the survey resided near open sewage or garbage mounds also containing remnants of the destructed structures.

The significant increase in BD and preterm births in 2016 compared to 2011, had no correlation with previous exposure of the mother to attacks in 2014 (43%). Rather, having babies with BD was significantly associated with nearness of the residence to places where garbage was burned in open air, and having BD and preterm babies were associated to residence near to open sewage, as shown in Table VIII.

Table 8: Percentage of mothers residing near risky locations and recalling exposure to attacks in 2014, in relationship with the outcome of their pregnancy.

outcome of pregnancy	Normal	BD	preterm
nearby open sewage presently	21,4	34,0**	28,9*
nearby burning garbage presently	6,3	11,3*	5,7
own house attacked in 2014	15,2	15,3	12,2
attack next door house in 2014	27,8	24,4	29,7
* p<0,05 **p<0,01			

The cohort of mothers which resided in proximity to military remnants had also significantly higher load of toxicants in their hair (Ba, V), teratogen (Hg) and carcinogen (Co), compared to those leaving far from these sources of contaminants (Table IX).

Table 9: The heavy metals whose load in mothers' hair was higher for residents near sewage and open burning of garbage that in the hair of those not near.

Metal		median	average	N	p value
Ba	near	7,79	30,7	25	0,0145
	not near	4,23	4,9	21	
Co	near	0,14	0,925	25	0,0137
	not near	0,11	0,24	21	
Hg	near	0,297	1,577	25	0,05
	not near	0,159	0,2	21	
V	near	0,908	1,147	25	0,0136
	not near	0,61	0,545	21	

Thus, in 2016 there was correlation between woman residence near risky deposit of war remnants, higher probability of having a BD or preterm baby and their higher load of contamination by specific heavy metals.

In the survey of births in 2018-19, no correlation was found between mother's exposures to previous military attacks with the metal load in their hair or with the outcome of pregnancy. In 2018-19 only 12% of the mothers still lived near war remnants.

Nonetheless, the prevalence of negative outcome at births did not decline from 2016 and the 95percentile values of concentration of the heavy metals, concerning for their toxicity or impact on health, were consistently higher than those of references, and, for most, similar as in the previous years (Table X).

Table 10: The 95 percentile values of the metal load of 12 toxic metals in the hair of the women in the cohorts registered in the years 2015-2019 compared to reference samples (in red). Highlighted in blue are the values significantly higher in the cohorts tested than in the reference control. For titanium and arsenic the 95percentile values become higher than control only since 2016.

Year	2015		2016		2018-19		Ref.
	95th pc	95% CI	95th pc	95% CI	95th pc	95% CI	
Metal							
Ba	29.69	24.0-49.1	44.6	31.9-187.1	29.9	17.6-1600.	<4.64
As	0.234	0.20-0.27	0.463	0.193-30.6	0.456	0.369-11.6	<0.2
Cd	0.24	0.2-0.3	0.66	0.43-1.2	0.97	0.50-2.6	<0.2
Co	0.57	0.37-0.76	1.68	0.99-6.8	13.1	1.7-33.0	0.01-0.30
Cr	2.91	2.53-3.3	3.73	2.7-12.1	4.4	3.3-7.4	0.01-0.20
Hg	1.63	1.1-4.8	2.16	0.94-20.5	0.76	0.26-22.4	<0.6
Mo	0.26	0.21-0.32	0.22	0.12-0.41	0.08	0.07-0.214	0.03-1.00
Se	0.88	0.86-0.95	0.75	0.51-9.1	1.16	0.88-26.1	0.40-1.70
Sr		136 122.3-160	201	109.8-436		166 124.3-418	0.65-6.90
Ti	0.82	0.73-1.0	2.75	1.5-5.6	3.1	1.7-6.1	<1.50
U	0.53	0.46-0.68	0.41	0.29-0.93	0.54	0.36-1.7	<0.10
V	1.4	1.26-1.56	1.8	1.3-6.5	1.4	1.1-2.0	0.01-0.20

Comparison of the median values of the load of these metals in women in time (Table XI) is more reflective of the diffusion in the population than the 95percentile values. Median values showed significant increase from 2015 to 2018-19 for some of them As, Cd, Co, Cr, Sr, Ti, U and V (highlighted in pink); decrease, only in 2018-19 for Hg and Mo, and decrease since 2016 for Se (highlighted in green); the level was unchanged for Ba.

Table 11: Comparison of the median metal concentration in hair of cohorts of mothers in the years 2015-2019.

year	2015 (N = 502)		2016 (N = 78)		2018-19 (N = 64)		p
	Median	IQR	Median	IQR	Median	IQR	
Ba	4.8	2.5-10.3	5.6	3.7-12.2	6.9	3.2-11.3	0.056
As	0.07	0.04-0.12	0.05	0.03-0.09	0.16	0.04-0.25	<0.001
Cd	0.05	0.02-0.09	0.15	0.07-0.23	0.14	0.09-0.23	<0.001
Co	0.05	0.02-0.13	0.11	0.04-0.20	0.20	0.07-0.63	<0.001
Cr	0.67	0.33-1.2	1.2	0.69-1.9	1.2	0.70-2.2	<0.001
Hg	0.19	0.10-0.35	0.29	0.13-0.44	0.01	0.0-0.08	<0.001
Mo	0.06	0.04-0.11	0.06	0.03-0.08	0.02	0.0-0.04	<0.001
Se	0.65	0.54-0.74	0.33	0.20-0.45	0.42	0.28-0.58	<0.001
Sr	49.2	32.0-75.0	51.1	36.2-76.1	66.5	44.4-89.3	0.018
Ti	0.26	0.16-0.41	0.59	0.28-0.92	0.34	0.04-0.69	<0.001
U	0.15	0.09-0.27	0.12	0.07-0.20	0.15	0.06-0.27	0.041
V	0.43	0.19-0.74	0.70	0.41-1.1	0.64	0.37-0.98	<0.001

This data confirms the patterns seen in comparing 95percentiles values, the resilience of these metals in the environment and the continuing assumption by the population in the post-war context up to 5 years from the last military attacks. They also confirm the increase above the control values of titanium and arsenic only from 2016.

The lack of correlation between mother exposure with birth outcomes in 2018-19 is compatible with the wider spread of heavy metals in the environment during the disposal of war remains that made them equally available to all. Chronic and diffuse exposure to the environmental toxicants flattened the differences in metal loads due to previous recent or locally confined sources of exposure. The wider

spread of contaminants in the environment "equalized" and stabilized at a high level the stochastic chances of negative events occurring during pregnancy

Analysis of the subgroup of newborn with birth defect in 2016 showed the presence of a higher load of titanium in their hair than in those of normal or preterm babies. Titanium, and Arsenic 95 percentile values were not different that control in the cohort tested only 6-9 months after the attacks of 2014, but their 95percentile values increased since 2016; the median values for Ti increased in 2016 and median values for As in 2018, as shown above in Tables X and XI.

In 2016, there was association of BD newborn with higher load in titanium than in the group of preterm babies, and with a slightly higher load in mercury, as previously found in 2011; preterm babies had higher loads than normal babies for a number of metals, noticeably including barium.

Table 12: Metal load in newborn hair in the year 2016 total sample is 60. Amounts in ppb are shown, for BD and preterm newborns and these are compared to each other and highlighted, in yellow= more than 2 fold, in grey more than 1,5 folds.

metals ppb	Ba	As	Cd	Cr	Hg
newb BD	0,178	0,0066	0,00278	0,1033	0,4909
newb Preterm	1,0997	0,0443	0,0339	1,7351	0,3027
metals ppb	Sn	Sr	Ti	U	V
newb BD	0,06	1,37	1,59	0,0005	0,0056
newb Preterm	0,4162	2,482	0,6561	0,0071	0,041
more than 2 folds		more than 1,5 folds			

In 2011 the value in ppb amounts of mercury (0.93 ppb) was higher than in 2016, but in both years was higher than in normal and preterm babies. The value of barium amounts in preterm babies in 2011 and 2016 were similar (1,07 and 1,09 ppb). Tin was much lower in 2016 in BD babies and for preterm babies, compared to newborns in 2011.

Cadmium amounts did not change in time, while chrome levels were 1,5 folds higher in 2016 than in 2011 only in preterm babies. Other metals tested 2011 did not differ in preterm or BD in their loads from normal babies.

These data suggest that, while there is consistent high load for some metals associated with BD or preterm outcomes, there may also be a difference in kind or/and amount of each metal in the weapons remnants from each successive war, that can also affect the negative outcomes at birth.



## 4 DISCUSSION

To date, no study has been produced of surveillance of reproductive health in any war area on a random cohort of relevant size accompanied by systematic parallel investigation of human contamination by heavy metals delivered by weapons and by objective verification of individual's exposures to war-related events, or of newborn contamination by heavy metals related to the kind of negative outcome at birth.

Also, there was no previous proof of fact and characterization of heavy metals delivered in the wounds by white phosphorus ammunitions and by not-fragmenting ammunitions, both weapons used in Gaza.

The main points of force and the novelty of the study are the consistent methodological approach of its design and data collection, its time frame allowing diachronic vision of the data, the multidisciplinary sources of information from which it draws.

Lack of these elements in previous reports, may be due to the limitations posed, by intrinsic and extrinsic factors, to investigations in a war or afterwar area.

### 4.1 Methodology in Data Collection and Multidisciplinarity

Methodologically, epidemiological studies on random cohorts of size adequate to the questions investigated, are the best if not the only way to eliminate biases. The elaboration of an appropriate questionnaire for birth survey, inclusive of environmental questions focused to the contemporary local context, in addition to the Eurocrat or WHO format, allows to ascertain synchronically the contribution of diverse environmental factors to reproductive health, and measure of metal contamination on the same random subset of population in which the epidemiologic outcomes are registered allows correlations between the two sets of information.

Methodologic consistence made possible to compare, diachronically, different sets of birth surveys and epidemiologic data, including the objectively verified recall of exposures by the individuals, and of measures of contamination by heavy metals.

The knowledge of the environmental situation and of its changes in time has been most valuable. Consultation with experts in other fields allowed to acquire knowledge often neglected or unavailable in this type of investigations, which proved very valuable for integration of the questionnaires of survey

in the course of the work, for validation of subjective recalls, and for interpretation purposes.

The knowledge of the precise chronology of the attacks and documentation of their places, and often also of the weaponry used, allowed the validation of recall of exposures by the women; that of the modalities of disposal of debris and of the length of time till they were unremoved, the modalities of recycling and places where it occurred, and the damages in the infrastructures, the lag in reconstruction, have been important factors for interpretation of the data in this study. The multispecialty collaborations also made possible to prove the delivery by weaponry to the ground in Gaza of defined heavy metals, and to give proof of fact of which of these metals are delivered in wounds.

The possibility we had to use a diachronic lens proved important for interpretation of data. It was very exceptional to have the privilege to pursue these studies along many years and with many colleagues in Gaza.

### 4.2 Summarizing and Concluding

The heavy metals delivered by various weaponry were identified and, in the limited types of ammunitions tested, were detected carcinogen, fetotoxic and toxic metals. In the case of metals embedded in the flesh at the site of the wound, they imprinted a molecular signature different for each type of clinically classified wound. Also white phosphorus ammunition delivered heavy metals in the wounds.

Nine months from the attacks in 2009, heavy metals were found in the hair of 60% of children in a random cohort covering all the Gaza strip.

At least since the first time they were tested for, in 2010, heavy metals delivered by weapons in the environment were assumed by the population, and since then there has been chronic exposure to war-remnants of the civilians. The level of heavy metals contamination in the population was shown to increased immediately in the individuals exposed to the 2014 military attack.

The measure of metal load in random cohorts of women in Gaza showed all the time that were tested since 2011, a higher 95 percentile value for metals associated to weaponry, by comparison with the reference, controls from outside the war area. Molybdenum instead was always lower than controls and titanium concentration increased over the control only in 2016. A similar pattern was found comparing in time of the median values of metal loads, thus ruling out the eventual relevance of spike values,

which confirmed a high background for weapon related heavy metals since 2011.

Still, above the high background, differences were found in the load of heavy metals according to exposures of the individuals to war related events and their residence. Association with these exposures persisted till 2016, when still 78% of the women resided near the rubble generated by attacks but was lost once the ruins were removed and pulverized in open air by 2018, and when only 12% of women resided near rubble. At this time the overall background contamination did not decrease, but the association between previous exposure and amount of individual contamination was lost.

The unchanged high load in metals in the population before and after removal of the war-remnants showed that environmental "remediation with reuse" of the war-remains, which was the only way accessible under siege and space confinement, may have contributed to the spread of contamination, but hardly to its decrease.

The role of exposure to attacks and war remnants on reproductive health was shown using more than one approach.

First, in general, the increase in prevalence in negative birth outcomes bridged wars. Spanning both the war in 2009 and the couple of wars 2012 and 2014 significant increase in BD was registered; also, prevalence in preterm births spiraled by 2016.

More in detail, the women with objectively documented exposures to military attacks or/and war remnants were those with higher probability to have a BD baby or preterm delivery and had the higher load in many heavy metals than their unexposed concitizens. This was associated to chronic assumption of metals, given that in all cases the women had kept residence for about 2 years in the same place of the attacks and of war remains thereof.

The cohort of 502 women tested for their metal load in the immediacy of the attacks in 2014 was not large enough to draw conclusions on the immediate effect of birth outcome of acute exposure to these.

The prevalence of negative birth outcomes remained in 2018-19 at the same level as in 2016, suggesting that by then a threshold level of "environmental factors", capable to sustain an unabated stochastic chance of negative birth outcome, was reached. At this time no association was found between recall of previous exposure to attacks or dwelling near rubble with birth outcome.

Chronic contamination of the mothers was accompanied, to differing extent for each metal, to passage in utero. Excess load of some metals was

found specifically associated in the hair of newborns either with BD or preterm outcomes.

Some contaminants associated specifically with BD or preterm were the same metals in comparable amounts in 2011 and 2016; these were respectively mercury and barium. and both times of testing were 2 years after a previous severe military attack.

Mercury was confirmed as inducer/co-inducer of BD, based on its high load specifically in hair of BD newborns, on the high load in the hair of mothers exposed to military attacks and war remnants in association with the higher incidence of BD progeny in this subgroup. Mercury remained significantly high compared to references controls throughout the years in the population, in parallel with high frequency of BD.

Barium was confirmed as inducer/co-inducer of preterm births, based on its high load specifically in hair of newborns of mothers exposed to weapons and military remains in 2011 and 2016. Barium remained significantly high in the population compared to references controls throughout the years, in parallel with higher frequency of preterm newborns.

In addition to high load of mercury for BD and of barium for preterm in 2011 and 2016, other contaminants were found in 2016 in newborns hair; specifically associated with BD, was titanium which was found in higher amounts than before in 2016; specifically associated with preterm were arsenic and chrome, also toxicants. Cadmium was not higher in the hair of BD or preterm babies in 2011, while was higher than normal in that of preterm babies in 2016. No comparison was possible between 2011 and 2016, for uranium and vanadium also higher in preterm in 2016, since these were not measured in 2011. Both these last metals do not trespass quantitatively the placenta but may have a role on the physiology of the mother, as does barium, and influence women capability to carry to term the pregnancy.

Recently Huang, 2021, examined in a cohort of Bangladeshi women the load for 56 metals and reported barium, titanium, and arsenic to be associated with preterm birth, but did not distinguish BD babies.

The relevance as direct effectors on BD and preterm outcomes of the heavy metals can be understood based on the known characteristic of their action and the epigenetic regulation of prenatal development by environmental factors [Perera, 2020; Torano, 2016; Dabre, 2006; Granjean, 2015; Cui, 2004)].

It is not known if other heavy metals, also chronically present in high amounts in the whole

population in Gaza, may act in synergy with the ones above in inducing effects on developmental health.

Thus, the use of diachronic lenses allowed to confirm which if the various metals detected as weapon-remnants may have a decisive role in determining the negative reproductive outcomes, even in compresence with other heavy metals contaminants, but also to visualize the possible "novel" relevance of metal effectors introduced, in kind or in relative amounts, through weapons modernization, as Gaza has been a "work in progress" as to the use of weaponry for the Israeli army.

Higher prevalence of BD and preterm babies since after 2011 translated in increase in newborn and infant death (Maartje, 2015), with costs for families and health care, and misery for parents and the affected child, even more pronounced when, as in Gaza, the possible interventions are themselves limited by the circumstances of the siege, imposing scarcity in economy, in medical and welfare supplies, and limitations in professional training. These limitations continue to endanger the chances of care for the BD and babies born preterm that survive. From these data, the level of increase in Gaza of major BD and preterm babies since 2011 translated in increase of about 1700/year additional newborn and infant deaths.

In addition, has been reported that the further development of children can be affected at various stages and levels (Vänskä, 2019) by Gaza's contaminated environment, as it happens in other places (Alvarado-Cruz, 2018); this is an issue that requires further studies and follow up.

Today, after another war in 2021 and the "preventive" attacks in 2022, the contamination by weapon remains will have increase, and the probability of heavy metals inducing negative birth outcomes may also have increased.

Finally, and the high load of heavy metals in the population may be also an effector of the reported increase in prevalence in Gaza of various non-communicable disease, infertility, cancers, and infective multiple antibiotic-resistant pathogens, affecting people of all ages and sex.

The population in the world whose health might be affected by negative long-term effects of the metal war-remnants amounts to some hundred million of people, and apparently war lords never take a break, while our common environment and bases of health continue to be devastated.

In a better world, where science could follow-up its work smoothly, and medicine could support the necessary development of safe care, the information provided here would be translated in actions.

Although main molecular mechanisms were already identified *in vitro* for the action of heavy metals, which include the accumulation of excessive reactive oxygen species, DNA damage, and over-activation of signaling pathways, shortening of telomeres, estrogen like action, binding to macromolecules and interference with key structural and enzymatic proteins, further investigations are needed on the role of the metals "candidate" here as inducers of BD, by testing their ability to affect cell differentiation, communication and growth and in model mammal's systems should be studied, in particular eventual key stages of the development during embryo and fetal development, the interference of heavy metals and the effects of exposure on the physiology of the placenta and on the proceeding of the pregnancy; it is needed to search for molecular biomarkers that result from exposure *in vivo* and which could be used to alert of the risks before/during human pregnancy. This work is costly and requires structured labs and, first of all, attention to the issue. But, in general, is possible at the state of the global art.

Meanwhile, it is necessary that clinicians identify substances potential "candidates for remediation" at first among the available pharmacopeia, e.g. among substance already widely used in pediatric age, tested for long time of usage, for lack of side effects on women, pregnancies, infants, and children; these should be molecules off-patent, and widely produced or product-able, so potentially affordable for prevention on population scale also in countries that have been already afflicted by wars.

At the same time, and in the better world that is surely coming, the documented testimony of long-term health damages by war-remnants presented here could catch the attention of the human right advocates and lawmakers and be considered as proof of fact of illegitimate use of weaponry with indiscriminate ray of action and documented consequences affecting civilians at large and used for whatever legal and international law implications there can be.

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