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Environmental Pollution and Its Association with Congenital Heart Disease: A Scoping Review

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Abstract

Introduction: Congenital heart disease (CHD) is the most common congenital anomaly in infancy affecting 1% of all live births worldwide of which the etiology in most affected children is unknown. The role of environmental pollutants from various sources is increasingly gaining attention. To explore the existing breadth of knowledge on this topic, we undertook a scoping review of studies examining the role of environmental pollution in relation to the development of CHD.

Methods: We searched various databases for studies reporting CHD and exposures to chemicals using Medical Subject Headings (MeSH) and non-MeSH including criteria pollutants (e.g. CO, SO_2, NO_2), occupational, non-occupational, industrial chemicals and emissions reported in pollutant release and transfer registers (PRTR) from 1980 to 2018.

Results: We identified 70 studies that were grouped into the categories of outdoor industrial chemical pollution; urban air pollution; occupational; and non-occupational exposures. There were no marked differences in proportions of studies in the first three categories, which ranged between 29-33%. Non-occupational exposures accounted for 7% of the studies. Proximity to industrial facilities and hazardous waste sites was associated with CHD in a modest number of studies that used PRTR. Urban criteria pollutants were consistently associated with CHD. Maternal occupational exposures were more commonly studied compared to paternal exposures and organic solvents were associated with CHD in these studies. There were limited studies that examined non-occupational and multipollutant exposures.

Conclusion: We identified associations between various chemicals and CHD, employing diverse methods of exposure assessment. Most studies examined single pollutant exposures and have demonstrated inconclusive findings. Future studies should examine multiple pollutant exposures and CHD. In addition to monitored data, exploratory studies could exploit PRTR in countries where such registers exist. Furthermore, multicenter studies that examine larger populations of affected patients could facilitate the discovery of the relationship between specific chemicals and CHD subtypes.

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Abbreviations:

APVR: Anomalous Pulmonary Venous Return; AS: Aortic Stenosis; ASD: Atrial Septal Defect; ATSDR: Agency for Toxic Substances and Disease Registry; AVSD: Atrio-Ventricular Septal Defect; CC: Case Control; CHD: Congenital Heart Disease; CO: Carbon Monoxide; CO2: Carbon Dioxide;

CoA: Coarctation of Aorta; DBP: Disinfectant by Products; DT: Developmental Toxicant; ECD: Endocardial Cushion Defect; HLHS: Hypoplastic Left Heart Syndrome; HWS: Hazardous Waste Site; LHO: Left Heart Obstruction; NGD: Natural Gas Development; NO: Nitrogen Oxide; NO_2: Nitrogen Dioxide; NPRI: National Pollutant Release Inventory; O_3: Ozone; PAH: Polycyclic Aromatic Hydro Carbon; PCE: Perchloroethylene; PDA: Patent Ductus Arteriosus; PM: Particulate Matter; PRTR: Pollutant Release and Transfer Register; RHO: Right Heart Obstruction; SO_2: Sulphur Dioxide;
TCE: Trichloroethylene; TCEQ: Texas Commission on Environmental Quality; TGA: Transposition of the Great Arteries; THM: Trihalomethane; TOF: Tetralogy of Fallot; TRI: Toxics Release Inventory; US EPA: United States Environmental Protection Agency; VOC: Volatile Organic Compound; VSD: Ventricular Septal Defect.

Introduction

Child health millennium developmental goals

At the beginning of the millennium, world leaders came together to formulate a vision to optimize the health of populations globally, particularly those exposed to extreme poverty and dehumanizing living conditions in countries with the lowest income per capita [1,2]. This gathering produced eight millennium developmental goals of which the fourth was aimed at reducing child mortality initially from infectious diseases, pneumonia, diarrhea, prematurity, birth asphyxia and neonatal sepsis by 2015 [3]. A progress report generated to track these achievements published in 2015 showed that whilst there was a marked reduction in the mortality of children less than five years of age down from 90 to 43 deaths per 1000 live births between 1990 and 2015, there was still room for more children's lives to be saved as expressed in the sustained developmental goals agenda [3,4].

Although the initial focus of the fourth millennium developmental goal did not include birth defects among the health issues targeted, it became clear with subsequent reviews, that birth defects are also important contributors to the ongoing mortality of infants and children of less than five years [5]. They concluded that a reduction in birth defects and optimization of the care of affected infants and children were necessary next steps if further reduction of child mortality were to be realized. Among all birth defects, congenital heart disease (CHD) remains the most common and the most serious birth defect worldwide [2,6]. Furthermore, severe CHD is recognized as a leading cause of disability due to long term sequelae even after treatment among infants which contributes importantly to costly health care for governments and families [7] and to the emotional stress of affected families [8-10].

Epidemiology of congenital heart disease

Globally, the prevalence of CHD has increased in the last century, beginning from 0.6 per 1,000 live births in 1930 to 9.1 per 1,000 live births after 1995 [11,12]. With an annual birth rate of 150 million worldwide, 1.35 million infants are born with CHD every year with highest rates of CHD observed in poor developing countries with high fertility and poor socio-economic circumstances [2]. The incidence of CHD may be even higher due to a substantial number of affected conceptions which end in missed abortion or fetal loss [6,13].

Greater strides in the surgical and medical management of CHD have been achieved during the last 60 years with longer life expectancy into adulthood even for patients with severe cardiac pathologies [13]. Although there are no accurate figures on the prevalence of adult congenital heart disease globally, it is estimated that there are at least 3000 per million adults with CHD globally [14]. A Canadian study conducted in Quebec, showed in recent years a higher prevalence of CHD in general amongst adults (57%) than children (11%) due to increased survival to adulthood [15]. A sub-analysis of severe CHD showed again a higher prevalence of CHD amongst adults (55%) compared to children (19%) [15]. This has now created a new challenge, that of a growing adult population with CHD which exceeds the number of affected children born who require ongoing medical attention from repeated hospitalizations for surgical, catheter or non-surgical interventions [15]. Consequently, the morbidity and mortality-related economic burden placed on healthcare systems, as well, as patients and their families are astronomical [7,16-19]. This economic burden underscores the urgency to identify the causes of CHD through collaborative research and innovative

methodologies that could lead to strategies to prevent these defects in our children.

The origins of CHD

Questions regarding the origins of CHD were articulated by Dr. Maude Elizabeth Seymour Abbott in the last century [20]. It is her framework that has guided researchers in this complex subject of the etiology of CHD to date. The mechanisms of teratogenicity are classified into two categories: 1) those that occur due to errors in genetic programming of the embryo, and 2) those due to environmental factors that interact with the embryo during cardiac morphogenesis prior to 7-8 weeks [21]. Approximately 15% of CHD are due to established genetic abnormalities which include single gene and larger chromosomal aberrancies [21,22]. Another 5-10% of CHD cases are believed to relate to known maternal conditions (e.g., diabetes, phenylketonuria) or teratogenic drug exposures (e.g. vitamin A derivatives) [22-25]. However, it is estimated that the combined non- inherited risk factors (e.g., diabetes mellitus, infections, teratogenic drugs.) account for at least 30% of CHD [26,27]. Still, a large proportion of the congenital heart defects fall into the category of unknown etiology, which is thought to be polygenic or fit the criteria of multifactorial disease [28,29]. Therefore, for almost half of the affected children, the cause of the CHD is not known, but it is thought to be related at least in part to complex interactions between parental exposures to environmental toxicants with or without genetic interplay [30-32]. The lack of sufficient and reliable information on what may constitute modifiable risks has contributed to the dearth of evidence-based strategies to reduce the burden of CHD [26,33-37].

The contribution of environmental pollutants from various sources in the development of CHD is increasingly gaining attention. To gain the breadth of knowledge generated from preliminary studies on this topic, we undertook a scoping review of the published literature on environmental chemical pollutant exposures and CHD development.

Methods

The following databases: Medline, CINAHL, Embase, Environment Complete, Scopus, Scifinder, Proquest dissertations were searched for studies on CHD and environmental chemical exposures from various sources to any media, e.g. occupational, non-occupational, industries, urban criteria pollutants [i.e., carbon monoxide (CO), sulphur dioxide (SO_2), nitrogen dioxide (NO_2), ozone and particulate matter (PM2.5 or PM10)], industrial emissions reported in pollutant release and transfer registers (PRTR).

We used individual or combination of keywords which included non-Medical Subject Headings (MeSH) and MeSH terms: ((heart defect* or heart disease* or cardiac defect* or cardiac disease*) and (congenital or newborn* or babies or baby or infant or infants)), "environmental pollut*", (prtr or prtrs or "release and transfer reg*" or "pollution release and transfer*" or toxic* release inventor* or npri or "pollution release and transfer*"or “air pollut*”, “chemical pollut*”, “occupat* exposure”). We included only original observational studies using cohort, case control or ecologic study designs written in English from 1980-2018. We excluded case reports, experimental studies, pharmacological studies, letters to the editor, systematic reviews and studies not reported in English. We extracted the information on the medium of exposure, authors, year of publication, study location, study design, study period, chemical pollutants examined, sources of pollutants and the findings from the studies.

Results

Figure 1 is a flow diagram illustrating the process of selection of the studies and Table 1 shows all the studies identified in the scoping review. We identified 337 original observational studies. After removing 12 duplicates, there were 255 studies that did not meet the inclusion criteria. A total of 70 studies were included in the final analysis and were grouped into the categories of occupational, non- occupational, industrial chemical pollution and urban air pollution studies shown in Figure 1. The characteristics of the studies examined are documented in Table 1. Most of the studies (87%, 61/70) used a case –control design to calculate odds ratios. Six out of 70 studies (9%) used an ecologic design, two (3%) used a retrospective cohort and one used a prospective cohort design. Table 2 shows the proportions of the exposure assessment methods employed in the studies. Most studies (34%) administered questionnaires to both mothers of a child with CHD and controls which were normal births followed by use of data from fixed

Table 1. Scoping review of environmental chemical pollution and the development of CHD.

Medium of Chemical Exposure	Author	Year	Study Location	Study Design	Study Period	Chemical Pollutants	Pollutant Data Sources	Findings
Maternal Occupation	Tikkanen et al.	1988	Finland	CC	1982-1984	Organic solvents:dyes, petrol, lacquers, paint, glues, wood preservatives, plastic, white spirit, anesthetic gases	Maternal interviews on solvent exposure	Organic solvents associated with VSD
	Tikkanen et al.	1988	Finland	CC	1980-1981	Type of Occupation	Maternal interviews	No associations with CHD
	Tikkanen et al.	1990	Finland	CC	1982-1983	Occupational exposures: organic solvents as above	Maternal interviews	Positive associations with organic solvents, alcohol
	Tikkanen et al.	1991	Finland	CC	1982-1983	Organic solvents as above,	Maternal interviews	Positive association with organic solvents
Maternal Occupation	Tikkanen et al.	1991	Finland	CC	1982-1984	Organic solvents: dyes, petrol, lacquers, paint, glues, wood preservatives, plastic, white spirit, anesthetic gases	Maternal interviews	No association found between the exposures and CHD

	Tikkanen et al.	1992	Finland	CC	1982-1983	Organic solvents as above	Maternal interviews	Positive association between conotruncal defects and organic solvents
	Tikkanen et al.	1992	Finland	CC	1982-1983	Domestic exposures to organic solvents as above, pesticides, disinfectants, maternal habits, ultrasound examination	Maternal Interviews	No association with CHD
Maternal Occupation	Tikkanen et al.	1992	Finland	CC	1982-1983	Organic solvents: (dyes, lacquers, paints), glues, plastic raw materials, wood preservatives, pesticides, anesthetic gases,	Maternal interviews	Organic solvents associated with VSD
	Tikkanen	1992	Finland	CC	1982-1983	Organic solvents: as above	Maternal Interviews	No association with ASD
Maternal Occupation	Tikkanen J et al.	1993	Finland	CC	1982-1983	Mineral oils, organic solvents	Maternal interviews	Mineral oils were associated with CoA

	Tikkanen J et al.	1994	Finland	CC	1982-1983	Organic solvents: (dyes, lacquers, paints), glues, plastic raw materials, wood preservatives, pesticides,	Maternal interviews	No association with HLHS
	Pradat P	1993	Sweden	CC	1982-1986	Maternal type of work	census data and medical birth registry	No association found with CHD
	Cordier et al.	1997	France, Italy, United Kingdom and Netherlands	CC	1989-1992	Glycol ethers	Maternal interviews	No association with CHD.
Maternal Occupation	Fixler et al.	1998	Dallas, Texas	CC	-	Maternal exposures to paint, organic solvents, varnishing, welding, lead, mercury, cadmium, arsenic, textiles and hair dyes, plastic, pesticides	Maternal interviews	No association with environmental exposures
	Bassili et al.	2000	Alexandria, Egypt	CC	1995-1997	Maternal or paternal exposure to organic solvents, printing, metal and textile industry occupation	Maternal interviews	Maternal or paternal hazardous occupation was associated with risk of CHD overall and VSD

Maternal Occupation	Loffredo et al.	2001	Baltimore-Washington Infant Study	CC	1987-1989	Exposure to pesticides for killing fleas, flying/ crawling insects, weeds and rodents at work or home.	Maternal interviews	Association of herbicides and rodenticides with TGA
	Gilboa et al.	2012	USA, NBDPS	CC	1997-2002	Occupational exposures to organic solvents	Maternal interviews	Associations between solvents and VSD, TGA, RHO, AS
	Lupo et al.	2012	USA, NBDPS	CC	1997-2002	Occupational exposures to PAHs	Maternal interviews	No association between PAHs and CHD
	Patel et al.	2012	USA, NBDPS	CC	1997-2005	Maternal exposures including occupational, smoking, alcohol	Maternal interviews	No association with AVSD
Maternal Occupation	Ou et al.	2017	China	CC	2012-2013	Maternal exposure to toxic trace elements and heavy metals	Maternal interviews and blood samples for analysis using inductively coupled plasma mass spectrometry	Lead was associated with CHD

Paternal Occupation	Olshan et al.	1990	British Columbia, Canada	CC	1952-1973	Firefighters exposed to: acrolein, benzene, CO_2, CO, dichlorofluoromethane, formaldehyde, hydrogen chloride, hydrogen cyanide, methylene chloride, nitrogen dioxide, sulfur dioxide, toluene,	Paternal occupation was linked with birth registration	Positive association with ASD and VSD
	Snijder et al.	2012	Netherlands	CC	2003-2010	Pesticides, phthalates, alkylphenolic compounds, polychlorinated compounds, heavy metals, bisphenol A.	Parental interviews on chemical exposures	Paternal exposures associated with CHD
Paternal Occupation	Correa-Villasenor et al.	1993	Baltimore – Washington Infant Study	CC		Type of work: jewelry maker, lead soldering, welding, paint stripping	Interviews	Associations between jewelry makers, lead soldering and septal defects. Welding associated with pulmonary atresia

	Aronson et al.	1996	Ontario, Canada	CC	1979-1986	Firefighters exposed to: acrolein, benzene, CO_2, CO, dichlorofluoromethane, formaldehyde, hydrogen chloride, hydrogen cyanide, methylene chloride, nitrogen dioxide, sulfur dioxide, toluene, trichloroethylene	Firefighter Registry	No association with CHD
Non-occupational Exposures	Forand et al.	2012	New York	Ecologic	1978 – 2002, 1983 - 2000	Indoor exposure to TCE, PCE and other VOCs through soil vapor intrusion	Sampling of indoor air for TCE, PCE and other VOCs	TCE and PCE associated with CHD, and conotruncal defects
	Liu et al.	2013	China	CC	2010-2011	Exposure to chemicals during house renovations e.g. marbles, plywood, laminated board, carpets, ceramic tile, oil-based paint, latex or acrylic coating.	Maternal interviews	Renovations associated with conotruncal and APVR defects

Non-occupational Exposures	Liu et al.	2015	China	CC	2010-2011	Exposure to lead-based sources	Maternal hair lead levels were measured by using inductively coupled plasma mass spectometry	Association between lead and CHD, septal, conotruncal, LHO and RHO defects
	Jin et al.	2016	China	CC	2010-2011	Exposure to arsenic, cadmium	Maternal hair arsenic and cadmium levels were measured by using inductively coupled plasma mass spectometry	Association between arsenic, cadmium and CHD.
	Liu et al.	2016	China	CC	2010-2011	Exposure to aluminum	Maternal hair metals measured as above	Association of aluminum with septal, conotruncal defects
Outdoor Industrial exposures	Malik et al.	2004	Dallas, Texas	CC	1979 - 1984	Exposure to hazardous waste sites (HWS)	US EPA	Associations with overall CHD and ECD when living within 1 mile of HWS.

	Yauck et al.	2004	Milwaukee, Wisconsin	CC	1997 - 1999	Proximity to trichloroethylene (TCE) emitting site	Toxics Release Inventory (TRI)	Association of older mothers exposed to TCE and congenital heart disease
	Kuehl et al.	2006	Baltimore Washington Infant Study	CC	1981 - 1989	Exposure to hazardous waste sites (HWS)	Toxics Release Inventory and National Priority List	HLHS cluster found in region with industrial emission of solvents, dioxin and polychlorinated biphenyls to air.
Medium of Chemical Exposure	Author	Year	Study Location	Study Design	Study Period	Chemical Pollutant	Pollutant data Source	Findings
Outdoor Industrial exposures	Batra et al.	2007	Washington	CC	1987 - 2003	Exposure to agricultural pesticides based on residence or occupation. Eastern Washington economy is dominated by agricultural industry	Birth certificates	Living in eastern Washington.Associated with VSD.
	Langlois et al.	2009	Dallas, Texas	CC	1996 - 2000	Proximity to HWS and industrial facilities	TRI, ATSDR Hazardous Substances Release/Health	Association found with truncus arteriosus

							Effect Database, TCEQ	
	Langlois et al.	2009	Dallas, Texas	Ecologic	1999 - 2003	Pesticides	Residence in an agricultural area	ASD associated with pesticides in rural regions.
Outdoor Industrial exposures	Gianicolo et al.	2012	Brindisi, Italy	Ecologic	2001 - 2010	Pollutants from petrochemical, manufacturing and power generating plants	Residence in high risk municipality	Increased risk of CHD
	Brender et al.	2014	Texas, USA	CC	1996 - 2008	Chlorinated solvents	TRI	TCE associated with septal defects
	Carmichael et al.	2014	California, USA	CC	1997 - 2006	Pesticides exposure	California department of pesticide regulation	TOF, HLHS, CoA, PVS, septal defects associated with pesticides
	McKenzie et al.	2014	Colorado, USA	CC	1996 - 2009	Proximity to natural gas development (NGD)	Colorado Oil and Gas Information System	CHD associated with NGD exposure to

	Wijnans et al.	2014	Netherlands	CC	2003 - onwards	Pesticides, phthalates, alkylphenolic compounds, heavy metals, polychlorinated compounds	Maternal interviews	Phthalates associated with VSD
Outdoor Industrial Exposures	Ngwezi et al.	2018	Alberta, Canada	Ecologic	2003-2010	Developmental Toxicants: Group 1 DTs (Benzene, CO, SO_2, carbon disulfide, toluene, 1,3 butadiene); Group 2 DTs (1,3 butadiene, chloroform, ethylene oxide, methanol, methyl-isobutyl-ketone, TCE); Group 3 DTs (arsenic, cadmium, hexachlorobenzene, lead, mercury).	National Pollutant Release inventory (NPRI)	Group 2 DTs associated with CHD and septal defects in rural regions

	Ngwezi et al.	2018	Alberta, Canada	Ecologic	2003-2010	Groups of DTs same as above. Exposure assigned to maternal postal code within 10 km of an emitting facility	NPRI	All DTs and the 3 groups of DTs associated with CHD in urban postal codes with the highest exposure. In rural regions, groups 1 and 3 associated with CHD in postal codes with highest exposure
Water pollution	Zierler et al.	1988	Massachusetts	CC	1980 - 1983	arsenic, lead, mercury, selenium, cadmium, chromium, silver, fluoride, nitrate and sodium	Monitored data from department of environmental quality engineering of the commonwealth of Massachusetts	No association with CHD. Arsenic associated with coarctation of aorta
	Swan et al.	1989	California	CC	1981 - 1983	1,1,1-trichloroethane, methyl chloroform	Solvent leak from manufacturing plant	No association with congenital heart disease

	Shaw et al.	1990	California	CC	1981 - 1983	Maternal water consumption during pregnancy	Maternal interviews on water consumption	No association of tap drinking water and congenital heart disease
	Goldberg et al.	1990	Tucson Valley	CC	1969 - 1987	Well water contaminated with TCE	Parental interviews	Positive association of TCE with congenital heart disease
Water pollution	Grazuleviciene et al.	2013	Lithuania	Prospective cohort	2007 - 2009	Maternal water uptake contaminated with trihalomethane (THM)	Measured THM from tap water samples for each water treatment plant	Brominated THM associated with increased risk of congenital heart disease
	Rudnai et al.	2014	Budapest	CC	1987 - 2003	Maternal exposure to arsenic in drinking water	Measured by water hygiene department	Association of arsenic with congenital heart disease PDA, ASD
	Sanders et al.	2014	North Carolina	Semi-Ecologic	2003 - 2008	Maternal exposure to arsenic, lead, cadmium and manganese from well water	Measurements from water well	High manganese levels were associated with conotruncal defects
	Kim et al.	2017	Texas	CC	1999 - 2005	Pesticide exposure (Atrazine) in drinking water		No associations between atrazine and congenital heart

								disease
	Wright et al.	2017	Massachusetts	CC	1999 - 2004	Disinfectant By Products (DBP) exposure in drinking water	Massachusetts EPA	Associations between DBP and TOF and septal defects.
Urban Air Pollution	Ritz et al.	2002	Southern California	CC	1987-1993	Data from ambient monitoring stations: CO, NO_2, ozone, PM10	Fixed site monitoring stations	Association between CO and VSD; and Pulmonary/ aortic artery anomalies and ozone
	Hansen et al.	2009	Brisbane, Australia	CC	1998-2004	Ozone, NO_2, SO_2, CO, PM10	Fixed site monitoring stations	Ozone associated with pulmonary artery and valve defects. SO_2 associated with aortic artery and valve defects. Inverse associations of CO and VSD and SO_2 with conotruncal defects
	Rankin et al.	2009	United Kingdom	CC	1985-1990	Black smoke, SO_2	Fixed site monitoring	No association with CHD.

							stations	
Urban Air Pollution	Strickland et al.	2009	Atlanta, Georgia	Retrospective cohort	1986-2003	CO, NO_2, PM10, SO_2, ozone	Fixed site monitoring stations	Associations between PDA and PM10.
	Dadvand et al.	2011	Northeast England	CC	1993-2003	PM10, SO_2, NO_2, NO, ozone	Fixed site monitoring stations	CO and NO associated with septal defects. CO associated with PV stenosis.
	Dadvand et al.	2011	Northeast England	CC	1985-1996	Black smoke, SO_2	Fixed site monitoring stations	No associations between SO_2 and CHD overall and subtypes
	Agay-Shay et al.	2013	Tel Aviv, Israel	Cohort	2000-2006	Ozone, NO_2, SO_2, CO, PM2.5, PM10	Fixed site monitoring stations	PM10 associated with multiple CHD
	Padula et al.	2013	California, USA	CC	1997-2006	Ozone, NO_2, SO_2, CO, PM2.5, PM10, traffic	Fixed site monitoring stations	PM10 associated with VSD, PVS. PM2.5 with TGA. Traffic with VSD
Urban Air Pollution	Gianicolo et al.	2014	Brindisi, Italy	CC	2001-2010	Ambient pollutant exposure to SO_2, NO_2 and TSP	Fixed site monitoring stations	SO_2 associated with congenital heart disease and VSD

	Schembari et al.	2014	Barcelona, Spain	CC	1994-2006	Exposure to traffic related pollutants: NO_2, PM2.5 and PM10	Land use regression models used to assign exposure to residential addresses of cases	NO_2 associated with CoA
	Stingone et al.	2014	North Carolina, USA	CC	1997-2006	Exposure to CO, SO_2, NO_2,ozone,PM2.5 and PM10	Fixed site monitoring stations	NO_2 associated with CoA and PVS. PM2.5 associated with HLHS.
	Hwang et al.	2015	Taiwan	CC	2001-2007	Exposure to CO, SO_2, NO_2,ozone and PM10	Fixed site monitoring stations	Ozone and PM10 associated with VSD, ASD and PDA
Urban Air Pollution	Jin et al.	2015	Lanzhou, China	CC	2010-2012	Maternal exposure to PM10, NO_2 and SO_2	Fixed site monitoring stations	PM10 and NO_2 associated with CHD and TGA. PM10 and SO_2 associated with septal defects. PM10 and NO_2 associated with PDA.
	Vinikoor-Imler et al.	2015	Texas	CC	2002-2006	Exposure to ozone, PM2.5	Fixed monitoring sites	No associations between ozone, PM2.5 and CHD

	Girguis et al.	2016	Massachusetts	CC	2001-2008	Exposure to traffic related air pollution	Satellite remote sensing, meteorological and land use data	No associations found with CHD
Urban Air Pollution	Vinceti et al.	2016	Milan, Italy	CC	2001-2008	Exposure to traffic related air pollution: PM10, benzene	Stationary plume dispersion model from the California LINE Source Dispersion Model Version 4	No association with CHD
	Yao et al.	2016	China	CC	2010-2012	Exposure to SO_2, NO_2 and PM10	Fixed monitoring stations	SO_2 associated with birth defects in the second trimester
	Zhang et al.	2016	China	CC	2011-2013	Exposure to PM2.5 and PM10	Fixed monitoring stations	Associations between PM2.5 and CHD
	Liu et al.	2017	China	CC	2007-2013	Exposure to PM10	Fixed site monitoring station	PM10 associated with ASD, VSD, PDA, and TOF and CHD.

Urban Air Pollution	Stingone et al.	2017	USA	CC	1997-2006	Exposure to traffic related air pollutants (TRAP), intake of methyl nutrients and CHD	Fixed site monitoring stations	Association of NO2 and VSD.

site monitoring stations (24%) and measurement of chemicals from tissue samples in 16% of the studies.

Table 2. Methods of Exposure Assessment Employed in the Environmental Pollution Studies.

Method of Exposure Assessment	Proportion n (%)	Study Design
Questionnaires	24 (34)	Case Control
Fixed site monitoring station	17 (24)	15 Case Control and 2 retrospective cohorts
Measurement of pollutants from samples	11 (16)	8 Case Control, 2 ecologic and 1 prospective cohort
Registries	8 (11.4)	7 Case Control and 1 ecologic
Proximity	5 (7)	4 Case Control and 1 ecologic
Residence in a polluted area	3 (4)	1 Case Control and 2 ecologic
Land use regression	2 (3)	Case Control
Dispersion modelling	1 (1.4)	Case Control

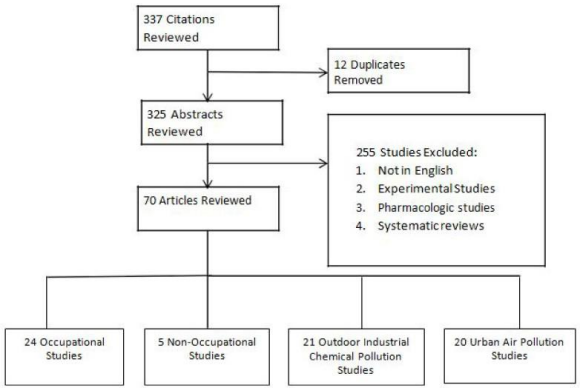

Figure 1. PRISMA flow chart illustrating the selection process of the studies.

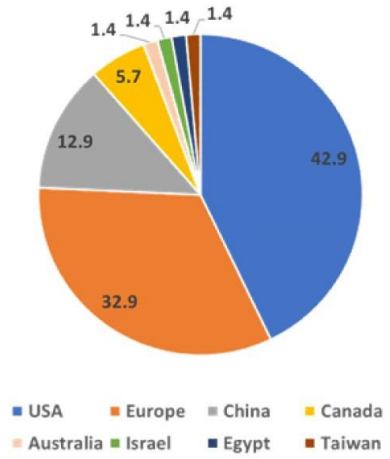

Figure 2. Proportions of the studies by region included in the scoping review by region.

Geographic distribution of environmental pollution studies and CHD

Thirty out of 70 (43%) of the studies were conducted in the United States followed by Europe (23, 33%) and China (9, 13%). There were four studies from Canada (6%) and one each from Australia, Israel, Egypt and Taiwan, as shown in Figure 2. Amongst the European studies, the bulk came from Finland and examined maternal occupational exposures and CHD.

Occupational exposures to chemical pollutants

Twenty-four of 70 studies (34%) investigated occupational exposures to chemicals and their associations with CHD. Twenty out of 24 (83%) studies examined maternal occupational exposures [23,24,34-50] and only 17% of the studies examined paternal exposures [51-54]. Maternal exposures to organic solvents such as lacquer, petrol, white spirit, alcohol, dyes and paints were associated with CHD overall, septal and conotruncal heart defects [23,34,36,38,45,47-49] and pesticides such as herbicides and rodenticides

were associated with risk of transposition of the great arteries [46]. One study found maternal exposure to phthalates was associated with ventricular septal defects [50]. One study examined maternal occupational exposure to trace elements such as selenium, chromium, copper and heavy metals such as lead, mercury and cadmium and found associations between lead and overall CHD and subtypes of CHD such as septal, conotruncal and right ventricular outflow tract obstructive lesions [54]. Among the four studies out of 24 (17%) that have examined the role of paternal exposures, two were Canadian studies of male firefighters exposed to mixtures of pollutants during emergency situations and found both positive [51] and negative associations with CHD [53]. A study by Loffredo et al. examined type of work (jewelry maker, welding, lead soldering, paint stripping) and found positive associations between jewelry makers and septal defects, lead soldering and pulmonary valve atresia [52]. The other study by Snijder et al., found associations between paternal exposures to phthalates and peri-membranous ventricular septal defects, alkylphenols and coarctation of the aorta and polychlorinated compounds and atrioventricular septal defects [55].

Non-occupational exposures to chemical pollutants

Very few studies (5/70, 7%) have examined non-occupational exposures in CHD development. One study which examined the relationship between house renovations and CHD found associations with conotruncal and anomalous pulmonary venous return defects [56]. Other studies examined heavy metals found in maternal hair (lead, cadmium, arsenic and aluminum) by measuring the chemicals in hair samples using plasma mass spectrometry, identified associations with septal, left heart obstructive, right heart obstructive and conontruncal lesions [57-59]. One other study demonstrated associations between soils contaminated by trichloroethylene (TCE) and tetrachloroethylene through soil vapor intrusion into the indoor environment and CHD [60].

Outdoor industrial chemical pollution

Twenty one of the 70 studies (30%) examined industrial chemical exposures through air or water and the development of CHD. Five of the 22 (23%) examined proximity to industrial sites as a proxy for exposure [61-65]. Seven studies (32%) used pollutant release and transfer registers (PRTR) [62-69]. Maternal residential proximity to hazardous waste sites [61,62], industries emitting organic compounds (e.g. TCE, natural gas development) were associated with CHD [63,64]. Another study explored residential proximity to industries and found associations between groups of known developmental toxicants (e.g. sulphur dioxide, TCE and mercury) and CHD in urban and rural regions with very high exposures [65]. Other studies which examined urban and rural differences in association with CHD found residence in rural regions to be associated with septal defects, and these were largely related to agricultural pesticide exposures [70-72]. In our recent work, we demonstrated the presence of rural vs. urban differences where we found a higher incidence of CHD and septal defects in rural regions which was associated with higher proportion of developmental toxicant emissions [66].

Other studies that examined industrial chemical exposures related to residence in various geographic areas, such as municipality or census tract that hosted hazardous facility or facilities, found associations with CHD [67,73]. Water contamination from industrial chemicals was a subject of nine of the 22 studies (41%). Metalloids such as arsenic and manganese were associated with coarctation of aorta and CHD overall [74-76]. The relationship between organic compounds in water and CHD has been less definitive with some reporting associations [77-79] and others reporting no association [80-82].

Urban air pollution

Twenty of the 70 studies included in the review (29%) investigated the role of urban air pollution and CHD in urban areas from sources such as traffic amd coal-fired power stations [83-102]. These studies examined criteria pollutants such as NO_2, SO_2, CO, O_3, PM2.5 and PM10 measured from fixed monitoring stations. The studies revealed heterogeneity in the effects found between the pollutants assessed and CHD development. All the studies represented case control studies and assigned exposure to the vulnerable window of cardiogenesis between the 3rd and 5th week post conception [103]. Generally, CO was associated with septal defects, pulmonary valve stenosis or pulmonary artery stenosis [83,88] but other studies

reported inverse associations between CO and ventricular septal and conotruncal defects [84]; NO_2 was associated with coarctation of aorta, pulmonary valve stenosis and patent ductus arteriosus [92,93,99,102] but others found no associations with CHD [96]; SO_2 was associated with aortic valve stenosis, septal defects, CHD [91,96,99] and others found no associations with CHD and its subtypes [85,88]; O_3 was associated with pulmonary valve stenosis, pulmonary artery stenosis, patent ductus arteriosus and septal defects [84,94] and no associations were found with CHD in other studies [86,87,100]; PM10 was associated with patent ductus arteriosus, pulmonary valve stenosis, ventricular septal defects, transposition of the great arteries, multiple CHD, tetralogy of Fallot [84,89,90,94,98,99] whilst other studies found no associations with CHD [83,95-97]; PM2.5 was associated with transposition of the great arteries, hypoplastic left heart syndrome and ventricular septal defects [90,93,97] and others found no associations [89,100]. One study by Stingone et al. examined multipollutant exposures from urban air pollutants and found associations with left ventricular outflow tract obstruction [93]. Some studies which examined traffic related exposures found that traffic density was associated with ventricular septal defects [90], however another study using traffic density found no associations with CHD [101]. Generally, most of the studies of urban air pollution used more specific CHD lesions likely as they offer a better resolution in the associations with the criteria air pollutants.

Discussion

The body of literature that examines the role of chemical pollutant exposures and CHD development has been expanding since the first published work from the Baltimore Washington Infant Study by Ferencz et al. [104]. However, the challenge is that it is difficult to make conclusive associations because these studies have employed various methodologies, explored various media of exposure, examined single pollutant exposures which make it difficult to make comparisons of the associations across studies.

We found that the predominant literature of chemical exposures assessed maternal occupational exposures, and these were conducted by a Finnish group of researchers as shown in Table 1. There were even fewer studies examining paternal occupational exposures and CHD development and yet the cause of CHD could lie in the aberration of the germ plasm of either one or both parents [20]. The studies focusing on occupational exposures and CHD explored organic solvent exposures likely as these chemicals are commonly found in occupational settings, industries and the environment [105]. For example, TCE which is an organic solvent has consistently been associated with CHD in observational and experimental studies [64,106].

Roughly one-third of the investigations have examined outdoor exposure to industrial chemicals. The few studies we found used proximity to industrial facilities as a surrogate for exposure. Even fewer studies have taken advantage of available PRTR in countries where they do exist and these studies did not incorporate the type or amounts of emissions reported in those registers except for two studies [65,66]. These registers offer the potential of examining multiple pollutant exposure as would occur in everyday life rather than single pollutant exposures which have been the subject of many studies to date. The role of multipollutant exposure in adverse health outcomes has been recognized as a new research direction that warrants investigation by the research community [107]. Only our study has examined multipollutant industrial chemical exposures to date
[65] and therefore there is still a need to explore further the relationships between multipollutant exposures and CHD.

Compared to other pollutant exposures, the level of evidence for urban criteria air pollutants (CO, NO_2, SO_2, O_3, $PM_{2.5}$ and PM_{10}) and CHD is more consistent particularly for NO_2, SO_2, PM_{10} and CO despite the heterogeneity of the associations amongst the CHD phenotypes. The advantage of these studies is that they have a precise spatiotemporal capacity to assign maternal exposure to pollutants during the vulnerable window of cardiac morphogenesis (3-5th) week post conception. Furthermore, in this group of studies, only a single previous study has attempted to examine multiple pollutant exposures using criteria air pollutants and found association with left ventricular outflow tract obstruction [93].

Most of the studies employed a case control design to calculate the odds ratios, whilst very few used an ecologic design or retrospective/prospective

cohorts. Exposure to chemicals was mostly assessed with administration of questionnaires after the adverse event had occurred to both mothers of a child with CHD and those with a normal birth followed by data from fixed site monitoring stations and some studies measuring the pollutants from tissue samples. The former approach poses a challenge of potential recall bias particularly for mothers who gave birth to a child with CHD or birth defect. There were very few ecologic studies most likely because of the known inherent limitations for assessing causality due to the "ecologic fallacy" that observations made at aggregate level cannot be inferred to individuals [108]. However, despite their limitations, for rare conditions such as CHD and with financial constraints, there is a need for more of these exploratory studies to provide preliminary hypotheses for further exploration in more robust designs [108].

Ultimately, the gold standard which would be prospective cohort studies of young women prior to bearing children would be more suitable for determining causality albeit more expensive. These studies could collect information on a wide range of antecedent environmental exposures in conjunction with tracking the mobility of mothers and personal monitoring of pollutant exposures using mobile devices. In addition, biomonitoring by collecting tissue samples such as urine, cord blood and placenta of infant-mother pairs or trio from both parents would provide strong evidence of a link between environmental exposures and CHD.

One limitation of CHD etiologic research is the lack of uniform and consistent methods of CHD classification [25], hampering comparisons. Most of the studies identified employed the World Health Organization's International Classification of Disease Code -9 which does not capture details on phenotypic heterogeneity of CHD. To overcome this problem, Botto et al., developed a comprehensive classification system based on clinical, epidemiologic and developmental considerations for use in CHD etiologic research. CHDs were described using three levels: 1) detailed anatomy, 2) aggregation into main group and 3) larger group based on developmental derivations. The adoption of this system by the research community would aid comparability of studies and achieving valid and precise estimates in risk factor analysis studies [25]. For example, organic solvents are the only chemicals recognized as having a definite association with CHD [26]. However, to gain more precision, unbiased estimates and attributable fraction of CHD from chemical exposures, multicenter studies could be conducted to increase sample size. Such an approach would also provide an opportunity to use a unified CHD classification system as suggested by Botto, which could facilitate discovery of potential mechanisms in which specific chemicals contribute to the development of specific types of CHD.

Conclusion

The reviewed literature predominantly identified associations between various chemicals and CHD, employing diverse methods of exposure assessment. We found that there was paucity of investigations examining multipollutant/mixtures of pollutants in relation to CHD development and yet human beings are exposed to many pollutants in the environment. There are modest numbers of studies which used the PRTR which have the potential to explore many chemicals. This approach could supplement the results of studies using monitored data. The evidence for the relationship between heavy metals and trace elements is sparse and inconclusive. There have been a paucity of studies examining non-occupational exposures from chemicals such as polycyclic aromatic hydrocarbons, polychlorinated biphenyl compounds, alkylphenols, perfluorinated compounds, heavy metals and trace metals amongst others and CHD development and the evidence is inconclusive. Furthermore, most studies examined maternal occupational exposures with few studies which examined paternal exposures to chemicals and CHD development and yet the chemical exposures may damage the germ plasm of the gametes of both parents. There are no studies using biomonitoring of chemicals from tissue samples to determine associations with CHD.

There is modest evidence, thus far, is based on few criteria pollutants from monitored data as these assign exposures at the precise critical window of cardiogenesis and thus mitigate against exposure misclassification. We conclude that future epidemiological studies should examine multiple pollutant exposures and CHD. In addition to monitored data, studies should exploit the PRTR in countries where such registers exist as they have the capacity to capture many chemicals which would

be costly to monitor in the environment. Prospective biomonitoring of birth cohorts, tracking of mother's mobility and personal monitoring of chemical exposures using mobile devices would increase the probability of discovering causal relationships in future studies.

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