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GLI EFFETTI DELL'INQUINAMENTO ATMOSFERICO NEI PRIMI 1000 GIORNI DI VITA SUL SISTEMA CARDIOVASCOLARE DEL BAMBINO. UNA REVISIONE DELLA LETTERATURA

A cura del gruppo di lavoro **"I primi 1000 giorni"**

Questo documento nasce nell'ambito del progetto Coorti di nuovi nati, esposizioni ambientali e promozione della salute nei primi 1000 giorni di vita: integrazione dei dati di esposizione con dati molecolari ed epigenetici (CUP: C92F17003030001)
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Gli effetti dell'inquinamento atmosferico nei primi 1000 giorni di vita sul sistema cardiovascolare del bambino. Una revisione della letteratura

Tabella 1. Strategia di ricerca utilizzata in PubMed

Database: Pubmed Date 01/03/2019		**N° record**
Exposure terms	"air pollution"[tiab] OR "air pollutant"[tiab] OR "air pollutants"[tiab] OR "sulphur dioxide"[tiab] OR "SO2"[tiab] OR "nitrogen oxide"[tiab] OR "nitrogen oxides"[tiab] OR "NOx"[tiab] OR "NO2"[tiab] OR ozone[tiab] OR "O3"[tiab] OR "particulate matter"[tiab] OR (PM*[tiab] NOT ("prospective memory" [tiab] OR postmenopaus*[tiab] OR "phosphamide mustard" [tiab]) OR "pregnancy morbidity"[tiab]) OR ("PAH"[tiab] NOT ("pulmonary arterial hypertension"[tiab] OR "Phenylalanine hydroxylase"[tiab])) OR "Volatile Organic Compounds"[tiab] OR ("VOC"[tiab] NOT "vaso-occlusive crisis"[tiab]) OR "black carbon"[tiab] OR "elemental carbon"[tiab] OR "organic carbon"[tiab]	**182289**
Outcome	"hypertension"[tiab] OR "blood pressure"[tiab] OR "Cardiovascular Diseases"[Mesh]	**2507743**
Population	Infant[tiab] OR newborn[tiab] OR toddler[tiab] OR child*[tiab] OR "Child"[Mesh] OR "Infant"[Mesh] OR preschool*[tiab] OR prenatal[tiab] OR pregnancy[tiab] OR birth[tiab] OR perinatal[tiab] OR gestation[tiab] OR fetal[tiab] OR "Adolescent"[Mesh] OR adolescent*[tiab] OR teen*[tiab]	**4288925**
	("Animals"[Mesh] OR "Plants"[Mesh] OR "Bacteria"[Mesh]) NOT "Humans"[Mesh]	**5485531**
	1 AND 2 AND 3	**1457**
	NOT 4	**1380**
	Filters activated: Child: birth-18 years.	**1028**
	Filters activated: Review, Child: birth-18 years	**53**

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Tabella 2. Tavola sinottica con descrizione delle 2 revisioni non sistematiche identificate sugli effetti dell'inquinamento atmosferico nei primi 1000 giorni di vita sul sistema cardiovascolare del bambino

Author, Journal, year	Subjects	Source, years, n of studies	Exposure	Outcomes	Results
Gorini F (2014) Pediatr Cardiol	children	7 studies included for the association between air pollution and Congenital hearth diseases	Air pollution	Congenital hearth diseases	Recent studies have shown an association between cardiac birth defects (i.e., ventricular septal defects; congenitalpulmonary valve stenosis) and maternal exposure to air pollutants, and specifically to CO, despite inconsistencies in the methods employed and the results reported (low level of evidence)

Kelishadi R (2014) Curr Probl Pediatr Adolesc Health Care	children	Not applicable	Air pollution	Cardiovascular diseases	The systemic responses to long-term exposure to air pollution could potentially increase the risk for development of cardiovascular diseases: - Exposure to air pollutants has many long-term effects on the beginning and progression of atherosclerosis from early life (5 studies); - A review of recent papers reported that exposure to ambient air pollution is considered to be associated with the development of non-alcoholic fatty liver disease, which is inter-related with metabolic syndrome and has common pathophysiological features with cardiovascular disease risk factors (4 studies); - the National Health and Nutrition Examination Survey (2003–2004) showed that environmental pollutants are associated with an elevation in serum alanine aminotransaminase level in a dose-dependent manner (1 study); - air pollutants exposure can cause intrauterine growth retardation, low birth weight, and prematurity which in turn can be associated with higher risk of chronic diseases as cardiovascular diseases in later life. - an accumulating number of studies support the role of vitamin D deficiency on cardiovascular diseases, type 2 diabetes, and metabolic syndrome, as well as on their underlying risk factors including obesity, dyslipidemia, insulin resistance, and hypertension. Literature suggests that one of the mechanisms of the harmful effects of air pollution on origins of cardiovascular diseases may be mediated through hypovitaminosis D.

Referenze

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- Kelishadi R. A review on the genetic, environmental, and lifestyle aspects of the early-life origins of cardiovascular disease. Curr Probl Pediatr Adolesc Health Care 2014;44(3):54-72.

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Tabella 3. Tavola sinottica con descrizione degli studi primari posteriori alla data delle revisioni non sistematiche

Author, year	Subjects	Type of study	Exposure	Outcome	Results
Huang CC (2019)	782 births reported to have CHDs between 2007 and 2014 and randomly selected 4692 controls without any birth defects using a population-based case-control design.	Case-control study from Taiwanese Birth Registry	Air pollution during early pregnancy. Data of exposure to ambient air pollutants, mainly PM2.5, PM10, CO, SO2, NO2, and O3 during weeks 3-8 of pregnancy were retrieved from air quality monitoring stations and interpolated to every township using ordinary kriging.	Congenital Heart Diseases (CHDs).	Positive correlation between increased PM2.5 exposure (adjusted odds ratio [aOR]=1.21, 95% confidence interval [CI]=1.03-1.42, per interquartile range change=13.4mug/m(3)) during early pregnancy and overall CHDs occurrence. Furthermore, we found that atrial septal defect (aOR=1.43, 95% CI=1.01-2.02), endocardial cushion defect (aOR=2.37, 95% CI=1.01-5.58), and pulmonary artery and valve stenosis (aOR=1.71, 95% CI=1.06-2.78) were significantly associated with PM2.5 exposures. No similar effects were observed for the other air pollutants.

Jung CR (2017)	Children < 5 years old with a diagnosis of KD from the Longitudinal Health Insurance Database 2000 (LHID2000) between 2000 and 2010.	Time-stratified case-crossover study	Carbon monoxide (CO), nitrogen dioxide (NO2), ozone (O3), particulate matter with aerodynamic diameter < 10 mum (PM10), and sulfate dioxide (SO2) from 70 monitoring stations; inverse distance weighting to calculate average daily exposures for the residential postal code of each case.	Kawasaki disease (KD) an acute and multi-systemic vasculitis	695 KD hospital admissions during the study period. An IQR increase (28.73 ppb) of O3 was positively associated with KD after adjusting for temperature, humidity, northward wind, and eastward wind [adjusted odds ratio = 1.21; 95% confidence interval (CI): 1.01, 1.44]. There were no significant associations between KD and CO, NO2, PM10, or SO2. The association with O3 was limited to exposure on the day of hospitalization and to exposure during the summer months (June-August).

Stingone JA (2017)	6,160 nondiabetic mothers	Case-control. Data from the National Birth Defects Prevention Study (United States, 1997-2006)	Maternal exposure to nitrogen dioxide (NO2), dietary intake of methyl nutrients. NO2 concentrations, a marker of traffic-related air pollution, averaged across postconception weeks 2-8, were assigned using inverse distance-squared weighting of air monitors within 50 km of maternal residences. Intakes of choline, folate, methionine, and vitamins B6 and B12 were assessed using a food frequency questionnaire.	Congenital heart defects in offspring.	Relative to women with the lowest NO2 exposure and high methionine intake, women with the highest NO2 exposure and lowest methionine intake had the greatest odds of offspring with a perimembranous ventricular septal defect (odds ratio = 3.23, 95% confidence interval: 1.74, 6.01; relative excess risk due to interaction = 2.15, 95% confidence interval: 0.39, 3.92).

Girguis MS (2016)	Massachusetts births conceived 2001 through 2008.	Case-control study	Particulate matter with diameter of 2.5microm or less (PM2.5); prenatal traffic-related air pollution. Satellite remote sensing, meteorological and land use data to assess PM2.5 and traffic-related exposures (distance to roads and traffic density) at geocoded birth addresses.	2729 cardiac, 255 neural tube, and 729 orofacial defects.	There were positive but non-significant associations for a 10microg/m(3) increase in PM2.5 and perimembranous ventricular septal defects (OR=1.34, 95% CI: 0.98, 1.83), patent foramen ovale (OR=1.19, 95% CI: 0.92, 1.54) and patent ductus arteriosus (OR=1.20, 95% CI: 0.95, 1.62). There was a non-significant inverse association between PM2.5 and cleft lip with or without palate (OR=0.76, 95% CI: 0.50, 1.10), cleft palate only (OR=0.89, 95% CI: 0.54, 1.46) and neural tube defects (OR=0.77, 95% CI: 0.46, 1.05). Results for traffic related exposure were similar. Only ostium secundum atrial septal defects displayed significant spatial variation after accounting for known risk factors.
Warren JL (2016)	Mothers from the National Birth Defect Prevention	Multinomial probit model in Bayesian setting	Maternal ambient air pollution exposure during critical periods of pregnancy (post-conception gestational weeks 2-8). Particulate matter less than 2.5 microm (PM2.5)	12 types of congenital heart defects	Association between increased PM2.5 exposure on post-conception gestational day 53 with the development of pulmonary valve stenosis and exposures during days 50 and 51 with tetralogy of Fallot. Significant associations are masked when using the aggregated exposure models.

Zhang B (2016)	Wuhan, China. 105,988 live-born infants, stillbirths, and fetal deaths. The study included mothers living in the urban district of Wuhan during pregnancy over the 2-year period from 10 June 2011 to 9 June 2013.	Cohort study	1-month and 1-week averages of PM10 and PM2.5 exposure based on measurements obtained from the nearest exposure monitor to the living residence of mothers during their early pregnancy period.	Congenital heart defects (CHDs).	Increased risk of CHDs, particularly ventricular septal defect (VSD), with increasing PM2.5 exposure. Using 1-week averages, significant monotonically increasing associations between PM2.5 exposure during weeks 7-10 of pregnancy and risk of VSD, with aORs ranging from 1.11 to 1.17 (95% CI: 1.02-1.20, 1.03-1.22, 1.05-1.24, and 1.08-1.26 separately) per a 10 mug/m(3) change in PM2.5 concentration.
Breton CV (2016)	768 college students recruited from the University of Southern California in 2007-2009.	Testing Responses on Youth (TROY) study. Historical cohort	Prenatal residential addresses were geocoded and used to assign prenatal and postnatal air pollutant exposure estimates using the U.S. Environmental Protection Agency's Air Quality System (AQS) database.	Participants attended one study visit during which blood pressure, heart rate and carotid artery arterial stiffness (CAS) and carotid artery intima-media thickness (CIMT) were assessed.	Prenatal PM10 and PM2.5 exposures were associated with increased CAS. For example, a 2 SD increase in prenatal PM2.5 was associated with CAS indices, including a 5% increase (beta = 1.05, 95% CI 1.00-1.10) in carotid stiffness index beta, a 5% increase (beta = 1.05, 95% CI 1.01-1.10) in Young's elastic modulus and a 5% decrease (beta = 0.95, 95% CI 0.91-0.99) in distensibility. Mutually adjusted models of pre- and postnatal PM2.5 further suggested the prenatal exposure was most relevant exposure period for CAS. No associations were observed for CIMT.

Breton CV (2016)b	459 participants as part of the Children's Health Study.	Cross sectional	Prenatal pollutants (PM2.5, PM10, NO2, O3), genetic and epigenetic features.	AluYb8 DNA methylation levels measured in newborn blood spot tests, and carotid intima-media thickness (CIMT) and blood pressure (BP)	Prenatal exposure to NO2 in the third trimester of pregnancy was associated with higher systolic BP in 11-year-old children. Prenatal exposure to multiple air pollutants in the first trimester was associated with lower DNA methylation in LINE1, whereas later exposure to O3 was associated with higher LINE1 methylation levels in newborn blood spots. The magnitude of associations with prenatal air pollution varied according to genotype for 11 SNPs within DNA methyltransferase 1 (DNMT1), DNA methyltransferase 3 Beta (DNMT3B), Tet methylcytosine dioxygenase 2 (TET2), and Thymine DNA glycosylase (TDG) genes. Although first-trimester O3 exposure was not associated with CIMT and systolic BP overall, associations within strata of DNMT1 or DNMT3B were observed, and the magnitude and the direction of these associations depended on DNMT1 genotypes.
Zeft AS (2016)	3009 Kawasaki disease (KD) residing in 7 metropolitan regions.	Case-crossover study design	PM2.5 exposure measurements from urban monitors to provide day-to-day temporal variability and resolution for time series indexes of exposures. Selected exposure windows (to 14 days) of PM2.5 were examined.	Fever onset for patients with Kawasaki disease (KD)	No evidence of a consistent, statistically significant, positive association between elevated PM2.5 exposure and increased risk of KD. Extended analysis with stratification by city, sex, age, ethnic origin, incomplete or complete clinical manifestations, the presence of coronary aneurysm, and intravenous immunoglobulin resistance did not provide evidence of a consistent, statistically significant, positive association between elevated exposure to PM2.5 and increased risk of KD for any of the strata studied.

Zhang B (2016)b	China. Mothers living in the central districts of Wuhan during pregnancy over the two-year period from June 10, 2011 to June 9, 2013.	Cross sectional	Maternal exposure to O3, SO2, NO2, CO	Congenital heart defects (CHDs)	In one-pollutant model, increased risk of CHDs, ventricular septal defect (VSD), and tetralogy of fallot (TF) with increasing O3 exposure. In two-pollutant model, associations with all CHDs, VSD, and TF for O3 were generally consistent compared to the models that included only O3, with the strongest aORs observed for exposures during the third month of pregnancy. Positive association between CO exposures during the third month of pregnancy and VSD in two pollution model.
Hwang BF (2015)	1087 cases of cardiac defects and a random sample of 10,870 controls from 1,533,748 Taiwanese newborns in 2001 to 2007.	Population-based case-control study	Ambient air pollutants (O3 and PM10) 4 categories-high exposure (>75th percentile); medium exposure (75th to 50th percentile); low exposure (<50th-25th percentile); reference (<25th percentile)	Cardiac birth defects	The risks of ventricular septal defects (VSD), atrial septal defects (ASD), and patent ductus arteriosus (PDA) were associated with 10 ppb increases in O3 exposure during the first 3 gestational months among term and preterm babies. In comparison between high PM10 exposure and reference category, there were statistically significant elevations in the effect estimates of ASD for all and terms births. In addition, there was a negative or weak association between SO2, NO2, CO, and cardiac defects.

van Rossem L (2015)	1,131 mother-infant pairs in a Boston, Massachusetts, area pre-birth cohort.	Cohort study	Average exposures by trimester and during the 2 to 90 days before birth for temporally resolved fine particulate matter (</= 2.5 mum; PM2.5), black carbon (BC), nitrogen oxides, nitrogen dioxide, ozone (O3), and carbon monoxide measured at stationary monitoring sites, and for spatiotemporally resolved estimates of PM2.5 and BC at the residence level.	systolic blood pressure (SBP)	Higher mean PM2.5 and BC exposures during the third trimester were associated with higher SBP (e.g., 1.0 mmHg; 95% CI: 0.1, 1.8 for a 0.32-mug/m3 increase in mean 90-day residential BC). In contrast, O3 was negatively associated with SBP (e.g., -2.3 mmHg; 95% CI: -4.4, -0.2 for a 13.5-ppb increase during the 90 days before birth).

Zhang M (2018)	1293 mothers in the Boston Birth Cohort (enrolled 1998-2012) and their children. Follow-up visits between 3 and 9 years of age	Cohort study	Ambient particulate matter ≤2.5 μm (PM2.5) concentration during pregnancy, estimated by matching mother's residential address to the US Environmental Protection Agency's air quality monitors.	Child systolic BP (SBP) percentile according to US reference (Fourth Report) and classified elevated BP as SBP ≥90th percentile.	Multivariable-adjusted cubic spline showed a sharp increase in offspring SBP percentile and risk for elevated BP when third-trimester PM2.5 concentration was ≥13 μg/m3 The highest versus lowest tertile of third-trimester PM2.5 exposure was associated with a 4.85 (95% confidence interval: 1.38-8.37) percentile increase in child SBP or a 1.61 (95% confidence interval: 1.13-2.30) times higher risk of child elevated BP. A 5-μg/m3 increment in PM2.5 during the third trimester was associated with a 3.49 (95% confidence interval: 0.71-6.26) percentile increase in child SBP or a 1.47 (95% confidence interval: 1.17-1.85) times higher risk of elevated BP.

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