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Exogenous Formaldehyde in the Exacerbation of Coronary Artery Disease: An Observational Study with Meta - Analysis

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Abstract: ***Background: Exposure to formaldehyde induces coronary artery disease (CAD) such as atherosclerosis, arrhythmia, tachycardia, ventricular or atrial fibrillation, stroke and it is linked to oxidative stress or inflammation. Higher concentrations of formaldehyde exposure can cause negative inotropic strength in the heart, sinoatrial dysfunction, which can result in bradycardia or death. The aim of this study was to identify the risk for cardiac events due to formaldehyde toxicity and to assess the transition in formaldehyde concentration. Materials and methods: For systematic review and meta-analysis, PubMed, EMBASE, ProQuest and Cochrane database were searched, by using the terms "formaldehyde and coronary artery disease". Studies addressed association between exposure to formaldehyde and cardiac events or hospital admissions / visits or incidence of myocardial infarction was the inclusion criteria. Studies published (English literature) from "January 2010 to August 2022" were included. The "Mantel–Haenszel Risk Ratio" was used for meta-analysis. For the observational component, the formaldehyde levels were obtained from a school and its peripheral areas based in west London and Margate in United Kingdom. The formaldehyde concentration was measured at 8:00 and 17:00 hours during 2018 to 2022. Results: Overall, 104 titles or abstracts were identified from the initial search, of which full manuscripts of 97 studies were retrieved, in the first phase. Later, 91 studies were excluded and six were subjected to meta-analysis. The mean formaldehyde concentration (daily exposure) across the studies ranged between 0.37 mg/m^3 to 5.4 mg/m^3. The majority (90%) of studies reported estimates for hospitalization due to formaldehyde including myocardial infarction. The risk ratio was 1.16 (95% C.I = 1.04 to 1.29) and hence for every unit (µg/m^3) increment in the formaldehyde concentration, contribute the risk for coronary artery disease (CAD). The observational component of this study reveals that, formaldehyde levels were unstable across the time points and it reduced in 2020. Conclusion: The risk for cardiac events due to formaldehyde toxicity was higher and the formaldehyde levels were dynamic. There was an association between formaldehyde exposure and CAD, including myocardial infarction and stroke. The formaldehyde concentration and longevity of exposure has a pivotal role in the exacerbation of CAD. Hence a critical evaluation of ECG / ECHO / cardiac markers should be performed among exposed cases to prevent further complications.***

Keywords: Cardiac dysfunction, exposure, risk factor, Myocardial Infarction

1. Background

Formaldehyde is a toxicant and it is the primary elements of anatomy dissection places and funeral areas.[1] Emissions from motor vehicles, incinerators, power plants, refineries are the major source of formaldehyde. It is also one of the byproducts of cigarette smoke.[2] Formaldehyde is commercially available as formalin, with a concentration of 37% by weight or 40% by volume of formaldehyde gas in water. The routes of exposure to formaldehyde are inhalation, ingestion, and dermal absorption.[1]

The formaldehyde levels in human cells can be 0.2 to 0.5 mM, and the concentration of it in the blood of healthy individuals is 0.05 to 0.1 mM. Hence, a low level of formaldehyde can be maintained in the blood and tissues by physiological or metabolic mechanisms.[3] Harmful effects of formaldehyde exposure, become more rigorous as its concentration level increases. The symptoms of exposure are dry or sore throat, itching and burning sensations of the nose, eyes, skin and nasal congestion. It can also exacerbate asthma, respiratory problems, dyspnea, and pharynx.[4]

Exposure to formaldehyde induces coronary artery disease (CAD) such as atherosclerosis, arrhythmia, tachycardia, ventricular or atrial fibrillation, stroke and it is linked to oxidative stress or inflammation.[3,5] Decrease in conduit vessel functions, following a 90-minutes formaldehyde exposure without any alteration to micro vascular function were reported among the studies. The oxidative stress marker malondialdehyde increased after the formaldehyde exposure. It can have deleterious implications for the vasculature and redox balance.[3]

The cardiomyocytes are sensitive to the toxicity of formaldehyde. Higher concentrations of formaldehyde can lead to negative inotropic strength in the heart. Direct exposure to formaldehyde can induce sinoatrial dysfunction, which can result in bradycardia or death from the sinus node syndrome.[5] In spite of the treatment regimens, the indicators

of cardiac dysfunction from formaldehyde are increasing. Thus, an estimate to quantify the risk of CAD by formaldehyde is intriguing.

Aim

To identify the risk for cardiac events due to formaldehyde toxicity and to assess the formaldehyde levels

2. Materials and Methods

The systematic review and meta-analysis identified the risk for cardiac events (CAD) due to formaldehyde exposure. Observational study concentrated to assess the transition in formaldehyde levels (µg/m^3) during 2018 to 2022 from a school and its peripheral areas based in west London and Margate in United Kingdom.

For systematic review and meta-analysis, the "PubMed, EMBASE, ProQuest and Cochrane library" were searched, by utilizing a combination of the relevant Medical Subject Heading (MeSH) terms and the key words "formaldehyde and Coronary artery disease". Studies addressed association between exposure to formaldehyde and cardiac events or hospital admissions / visits or incidence of myocardial infarction (MI) was the inclusion criteria. Studies published (English literature) from "January 2010 to August 2022" were included. The studies conducted on adult patients irrespective of study setting and regions were included. Animal studies, case reports, case series and those with insufficient data were excluded.

Search strategy

If studies reported cardiac events due to formaldehyde toxicity, then the full manuscripts were obtained. Selection criteria were applied to each of these studies and valid studies were subjected for final data extraction.

Quality appraisal

All the included studies were subjected to critical appraisal using the "Cochrane risk of bias assessment tool" for Randomized Controlled Trials (RCTs).[6] Each criterion was appraised as "Lower Risk of Bias", "Higher Risk of Bias" and "Not reported" [Figure 1]

Data analysis

The "Mantel–Haenszel Risk Ratio" (Fixed effect model) was used for meta-analysis. The "Chi- square, Tau^2 and I^2 statistic" were used to test heterogeneity.[7] "Review Manager Software (Rev Man 5, Cochrane collaboration, Oxford, England)" was used for data analysis.[8]

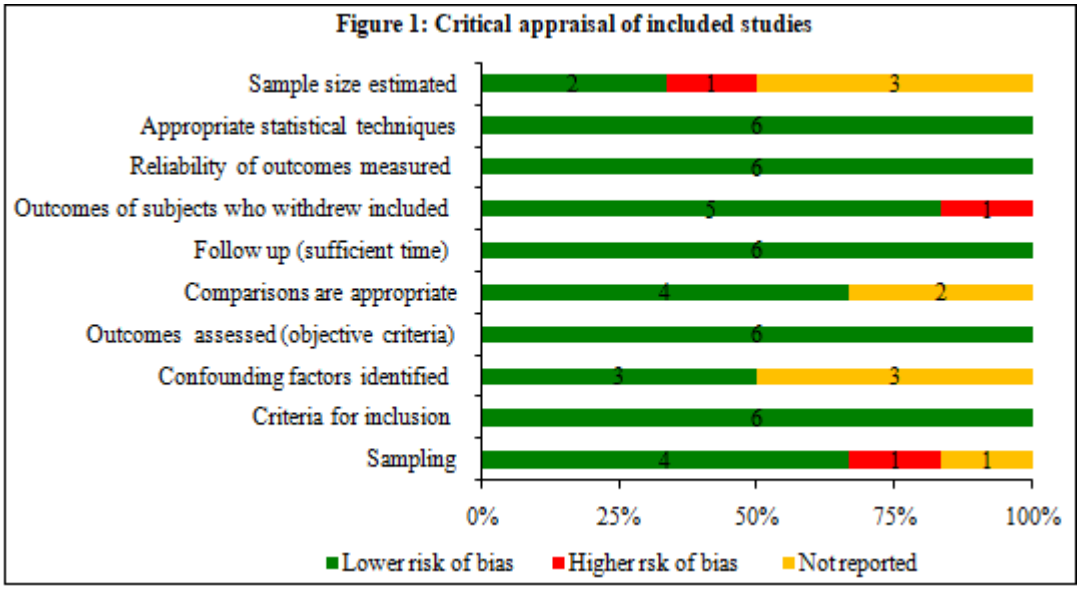
Transition in formaldehyde levels (Observational study)

The formaldehyde levels were obtained from laboratory (science) / library and garden areas of the one of the west London schools / Chiswick Park centre and its peripheral areas of London / Chiswick High Road / Chiswick residential road & garden / Margate hospital park, London. The formaldehyde was measured at 8:00 and 17:00 hours during 2018 to 2022. Paired "t" test ($p < 0.05$ as significant) was used to compare the formaldehyde concentration between the two time points for each year. Data were analyzed by using the SPSS software (SPSS Inc.; Chicago, IL) version 26.0.

3. Results

Overall, 104 titles or abstracts were identified from the initial search, of which full manuscripts of 97 studies were retrieved, in the first phase. Later, 91 studies were excluded and six were subjected to meta-analysis.[9-14] [Figure 2]. Mean formaldehyde concentration (daily exposure) across the studies ranged between 0.37 mg/m^3 to 5.4 mg/m^3.

Figure 1: Critical appraisal of included studies



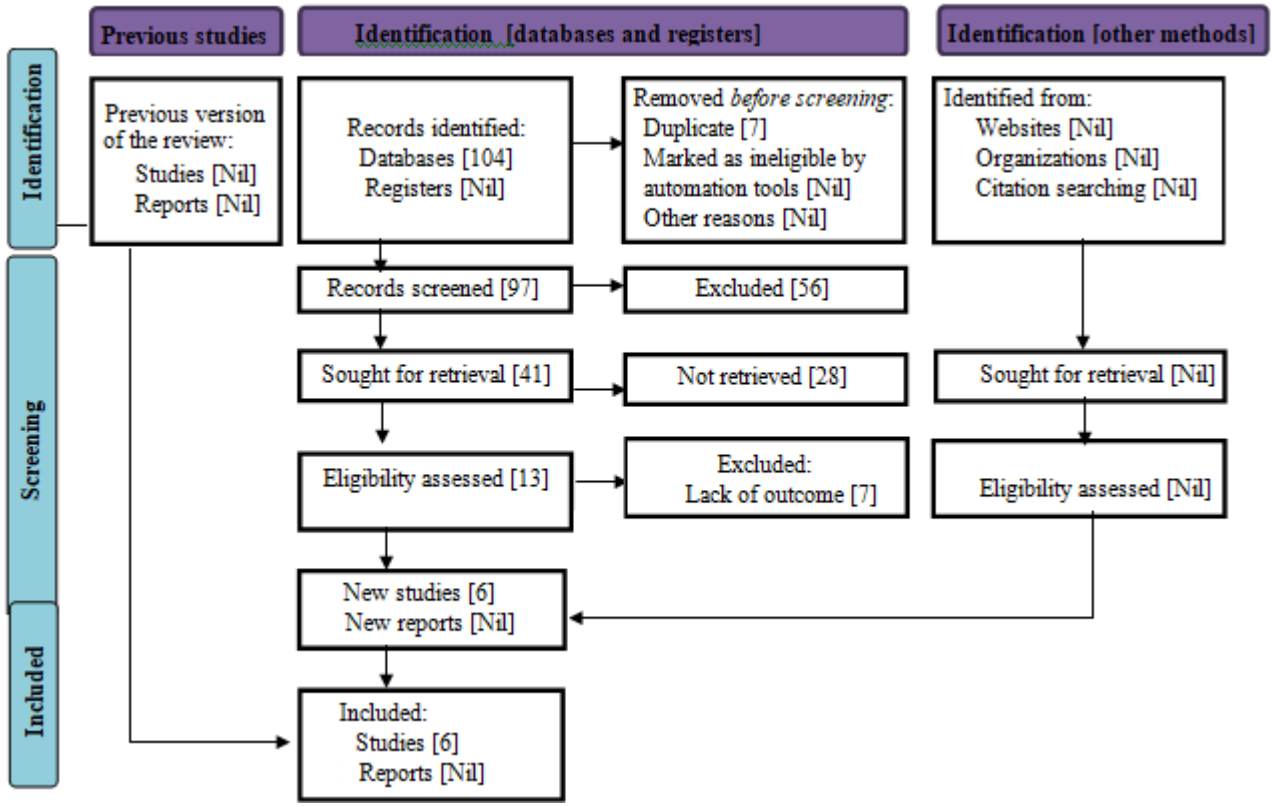


Figure 2: Flow-diagram [PRISMA-2021]

The risk ratio was 1.16 (95% C.I = 1.04 to 1.29) and hence for every unit (µg/m^3) increment in the formaldehyde concentration, there was a higher risk for CAD [Figure 3]. There was a homogeneity for the overall risk estimate (Tau^2 = 0.916) [Figure 4].

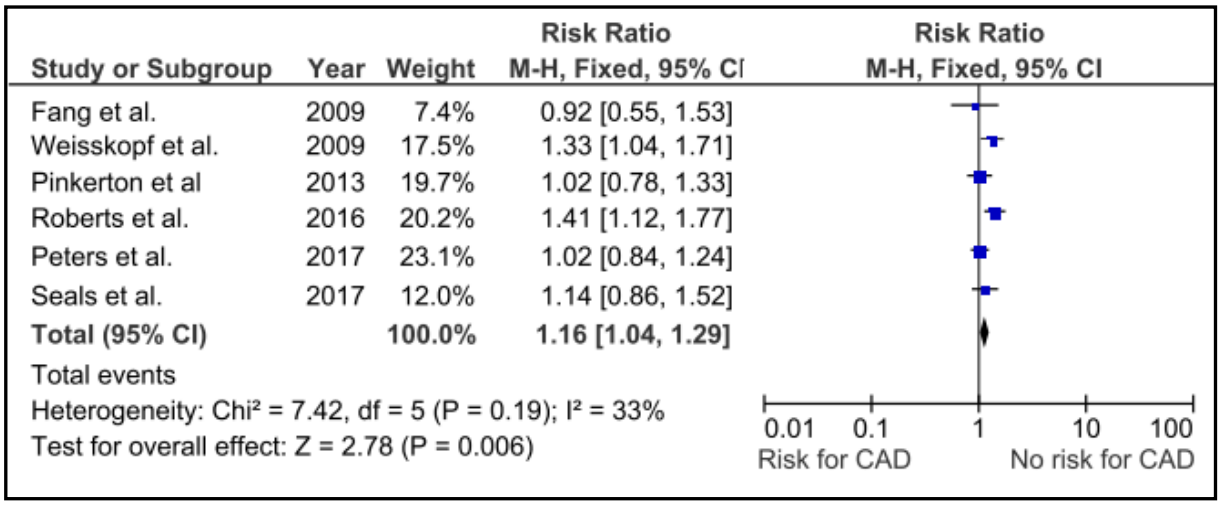


Figure 3: Risk of CAD due to formaldehyde exposure

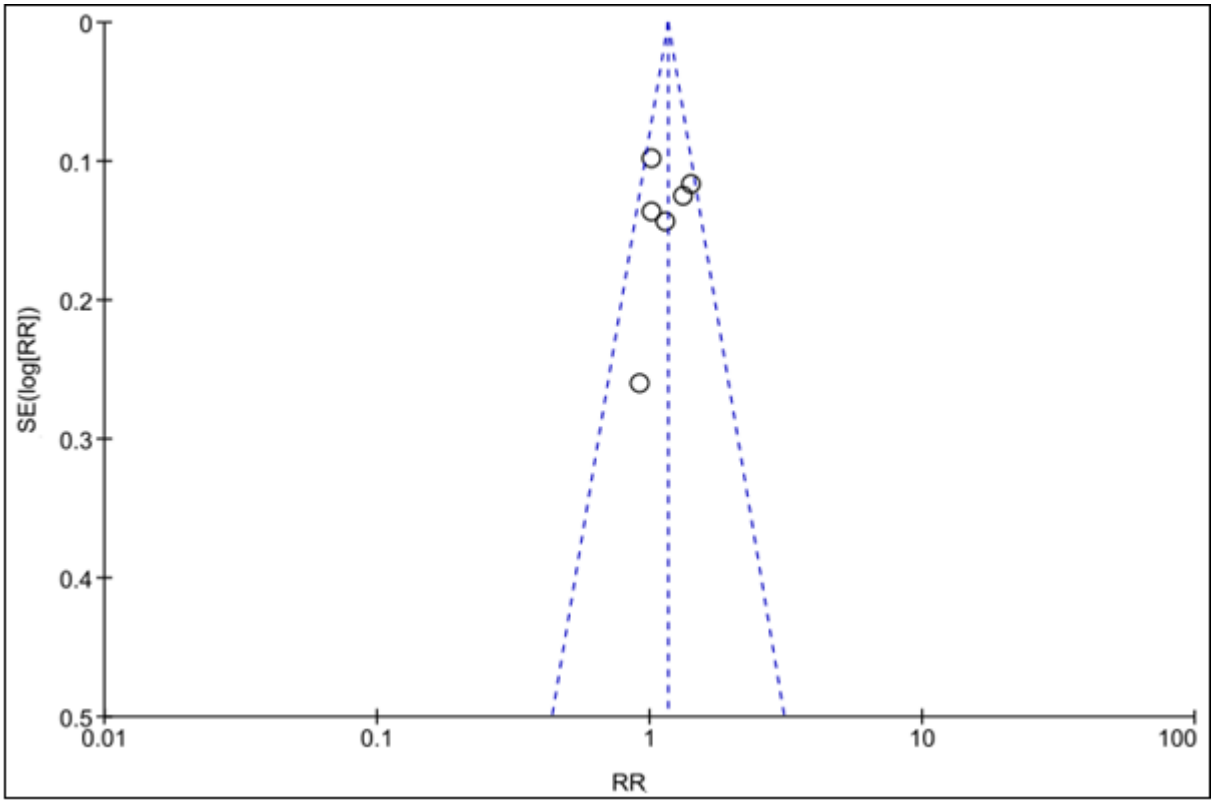
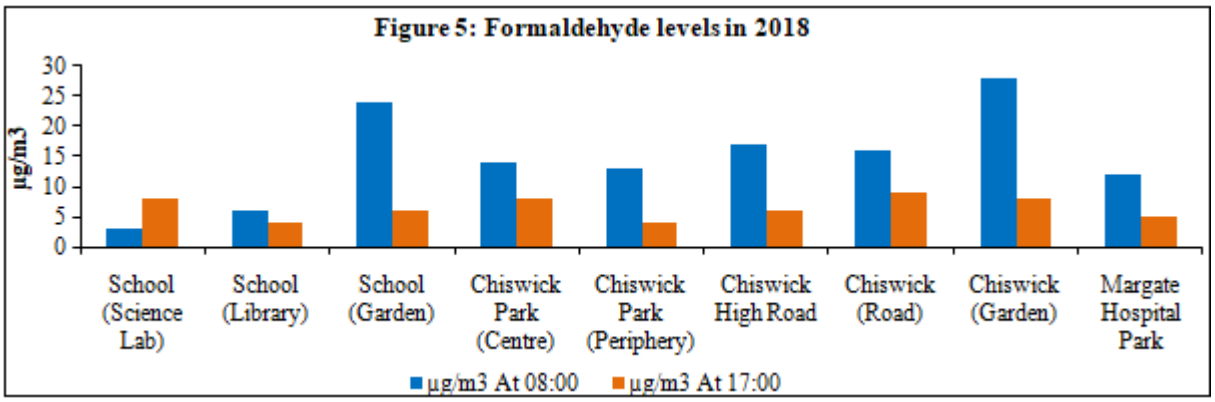
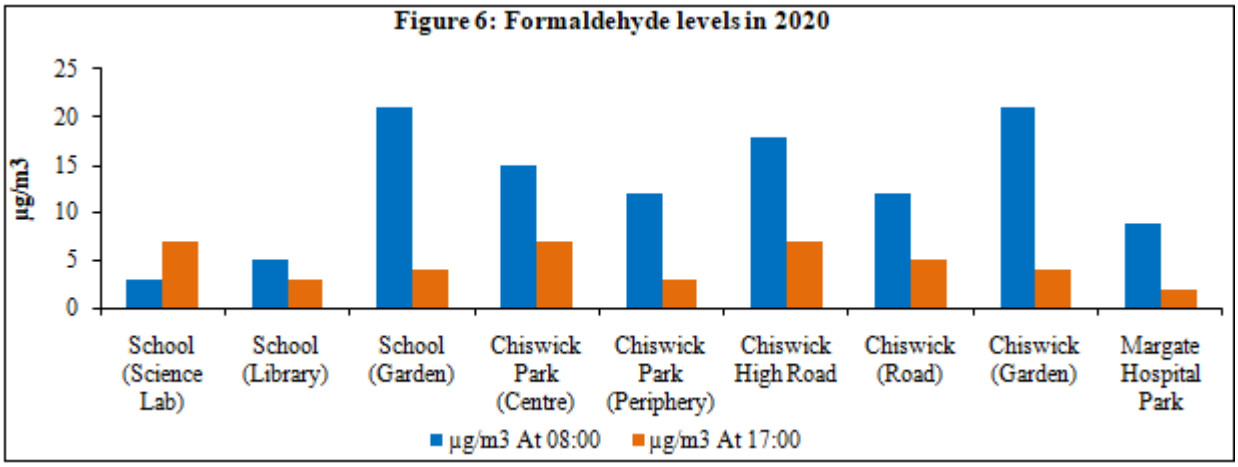


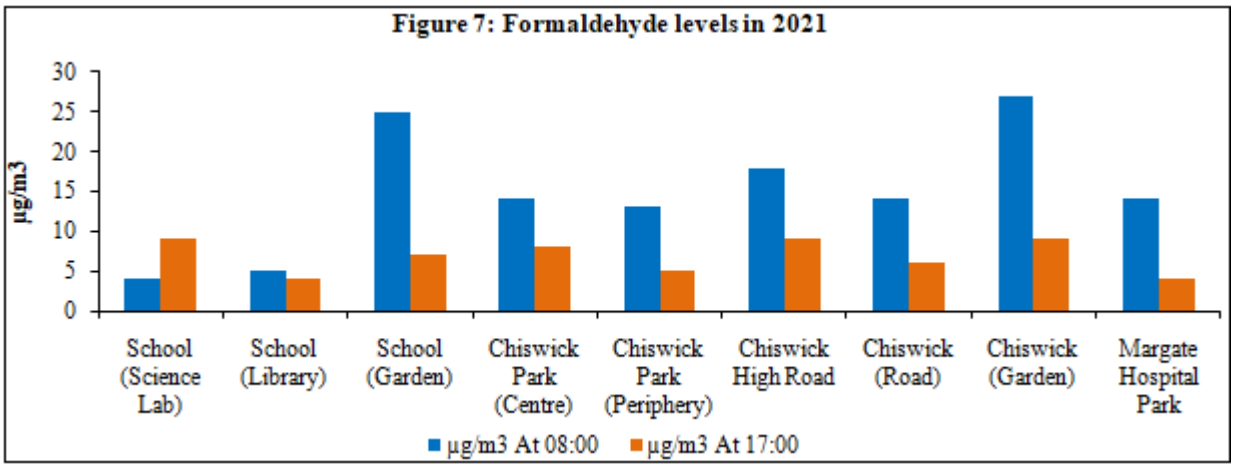
Figure 4: Funnel plot

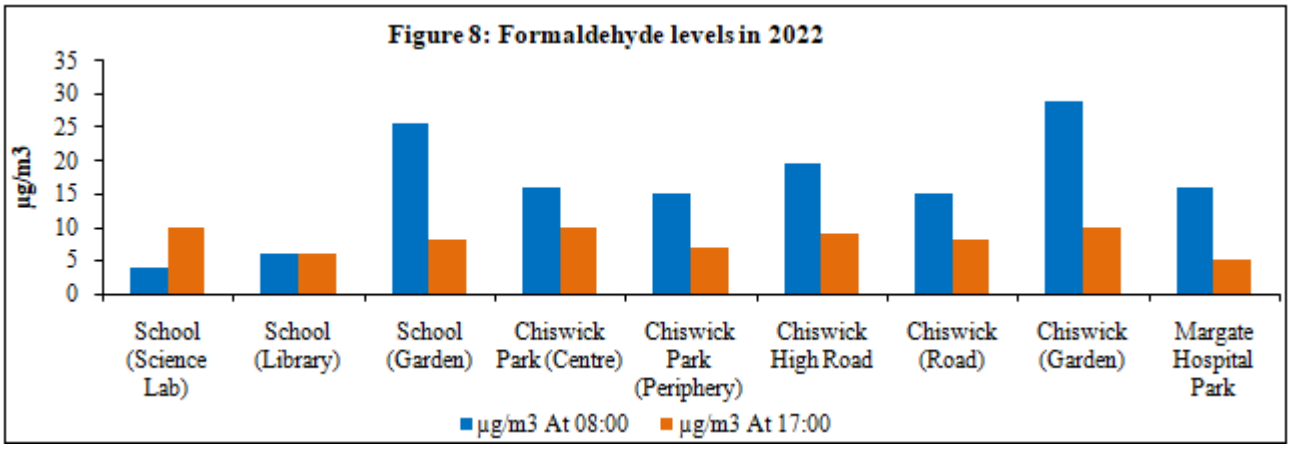
Transition in formaldehyde levels (µg/m^3)

The formaldehyde concentrations were obtained from a school and its peripheral areas based in west London and Margate in United Kingdom. Measurements were collected at 8:00 and 17:00 hours during 2018 to 2022. Data were summarized separately for school and its peripheral areas for each year [Figure 5-8]. The formaldehyde levels were unstable across the two time points (8:00 and 17:00 hours) during 2018 to 2022 and it reduced in 2020.





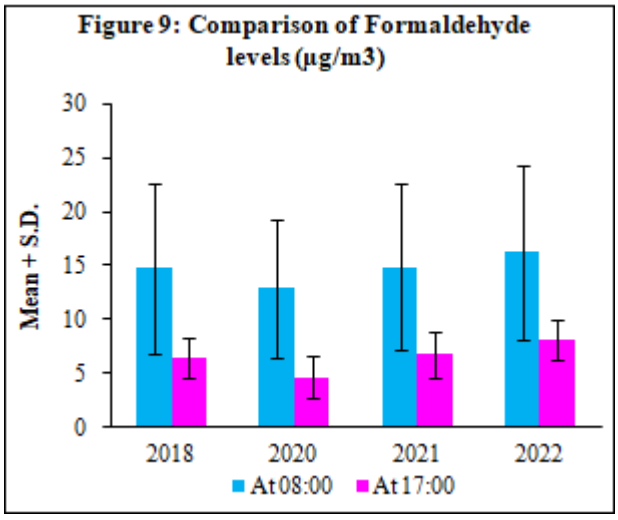




There was a difference ($p < 0.05$) in formaldehyde concentration between the two time points (At 08:00 and 17:00 hours) during 2018 to 2022 [Table 1; Figure 9].

Table 1: Comparison of formaldehyde (µg/m^3) levels

	At 08:00		At 17:00		"t"	p value
	Mean	S.D.	Mean	S.D.		
2018	14.8	7.9	6.4	1.9	3.283	0.011*
2020	12.9	6.5	4.7	1.9	3.708	0.006*
2021	14.9	7.8	6.8	2.1	3.331	0.010*
2022	16.2	8.0	8.1	1.8	3.105	0.015*



4. Discussion

In this review, the combined estimate across six studies contributed the risk for CAD including MI as 1.16 for every unit (µg/m^3) increment in formaldehyde. The risk for cardiac events due to formaldehyde toxicity was higher and the formaldehyde levels were dynamic. The histopathological or morph metric changes are linked with the duration of formaldehyde exposure and are associated with respiratory illness, lung injury, or CAD.[1] Formaldehyde induces oxidative stress, which is one of the detriments to respiratory or testicular tissues. The exposure has carcinogenic effect in the upper respiratory tract.[15]

The toxic effects of formaldehyde exposure can cause carcinogenesis and cardiovascular dysfunction, resulted by the DNA–protein formation. The upper airway irritation was found after exposure to formalin at most (95%) of it is absorbed through the upper respiratory tract. Sore throat, itching or burning sensations, and nasal congestion are the common symptoms of upper airway irritation.[16] The toxicity of formaldehyde aggravates upper airway dysfunction and exacerbates the susceptibility to arrhythmia, lung injury, and CAD.

5. Limitations

The formaldehyde may correlate with carbon monoxide / nitrogen dioxide / sulfur dioxide and it can be a confounder in the observed risk.

6. Conclusion

There was an association between formaldehyde exposure and CAD, including myocardial infarction and stroke. Hence a critical evaluation of ECG / ECHO / cardiac markers should be performed among exposed cases to prevent further complications.

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