Fine particulate matter-induced cardiac developmental toxicity (Review)

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Abstract. Fine particulate matter ($PM_{2.5}$) has become an important risk factor threatening human health. Epidemiological and toxicological investigations have revealed that $PM_{2.5}$ not only leads to cardiovascular dysfunction, but it also gives rise to various adverse health effects on the human body, such as cardiovascular and cerebrovascular diseases, cancers, neurodevelopmental disorders, depression and autism. $PM_{2.5}$ is able to penetrate both respiratory and placental barriers, thereby resulting in negative effects on fetal development. A large body of epidemiological evidences has suggested that gestational exposure to $PM_{2.5}$ increases the incidence of congenital diseases in offspring, including congenital heart defects. In addition, animal model studies have revealed that gestational exposure to $PM_{2.5}$ can disrupt normal heart development in offspring, although the potential molecular mechanisms have yet to be fully elucidated. The aim of the present review was to provide a brief overview of what is currently known regarding the molecular mechanisms underlying cardiac developmental toxicity in offspring induced by gestational exposure to $PM_{2.5}$.

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Abbreviations: $PM_{2.5}$, fine particulate matter; CHD, congenital heart defect; Mef2c, myocyte enhancer factor 2C; PAHs, polycyclic aromatic hydrocarbons; Pb, lead; Zn, zinc; Ti, titanium; Cr, chromium; Mn, manganese; As, arsenic; Ba, barium; Rb, rubidium; Ni, nickel; SERCA2A, sarcoplasmic/endoplasmic reticulum Ca^{2+}-ATPase 2A; NCX, sodium (Na^+)/Ca^{2+} exchanger; Cav1.2, voltage-gated Ca^{2+} channel; OS, oxidative stress; ROS, reactive oxygen species; RNS, reactive nitrogen species; AhR, Aryl hydrogen receptor; EOM, extractable organic matter; Nrf2, nuclear factor erythroid 2-related factor 2; GST, glutathione S-transferase; CAT, catalase; HO-1, heme oxygenase-1; NAC, n-acetylcysteine; Cyp1a1, cytochrome P450, family 1, subfamily A, polypeptide 1; iNOS, inducible nitric oxide synthase; NLRP3, NLR family pyrin domain containing 3; MerTK, marrow epithelial reproductive receptor tyrosine kinase; TNF, tumor necrosis factor; ICAM-1, intercellular adhesion molecule-1; NO, nitric oxide; MAPK, mitogen-activated protein kinase; JNK, c-Jun N-terminal kinase; NF-κB, nuclear factor-κB; mtDNA, mitochondrial DNA; ERS, endoplasmic reticulum stress; mPTP, mitochondrial permeability transition pore; mtROS, mitochondrial ROS; OPA1, OPA1 mitochondrial dynamin-like GTPase; Drp1, dynamin-related protein 1; Fis1, fission 1; M6A, N^6-Methyladenosine; Cd, cadmium; TCDD, 2,3,7,8-tetrachlorodibenzo-p-dioxin; DNAm, DNA methylation; DNMT1, DNA methyltransferase 1; DE, diesel exhaust; HMC, hydroxymethyl-cytosine; MBPs, methyl binding proteins; HATs, histone acetyltransferases; GATA4, GATA binding protein 4; CHOP, C/EBP homologous protein; mTOR, mammalian target of rapamycin; UPR, unfolded protein response; AhRR, AhR repressor; ESCs, embryonic stem cells; H3K79me2, H3K79 di-methylation; 8-OHdG, 8-hydroxydeoxyguanosine; BBC3, Bcl2 binding component 3; OGG1, 8-oxoguanine glycosylase; MTH1, MutT homolog 1; V, vanadium; S, sulfur

Key words: $PM_{2.5}$, cardiac, developmental toxicity, gestational exposure, heart defect

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1. Introduction

Environmental fine particulate matter of diameter ≤2.5 μm ($PM_{2.5}$) possesses small volume, large surface area, and is able to absorb harmful substances. It is a mixture consisting of various particles including organic, inorganic, metal and trace elements, and has become an important risk factor threatening human health (1,2). There is evidence to suggest that the toxicity of $PM_{2.5}$ varies depending on its components (3-5). The organic compounds in $PM_{2.5}$, including polycyclic aromatic hydrocarbons (PAHs), have attracted widespread attention due to their association with developmental toxicity (6). Moreover, $PM_{2.5}$ can easily enter the circulatory system and cross the placental barrier, thereby exerting negative impacts on fetal development (7). Congenital heart defect (CHD), the most common congenital defect in humans, accounts for ~1% of all live births (8).

As the first organ to form, the heart is extremely sensitive to environmental stress during embryonic development (9). The exact mechanisms underlying CHD have yet to be fully elucidated, although they are currently considered to arise as a consequence of the combination between genetic and environmental factors (10). Gestational exposure to $PM_{2.5}$ has been reported to be closely correlated with the occurrence of CHD in offspring (11-14). $PM_{2.5}$ is one of the major air pollutants in the world, posing a huge threat to human health. It is estimated that air pollution caused 9 million premature deaths in 2015, accounting for 16% of the global death toll, with 1.2 million deaths induced by $PM_{2.5}$. In fact, environmental pollution has become the leading cause of reversible death and disability resulting from cardiovascular diseases or cancers. Animal studies have also demonstrated that exposure to $PM_{2.5}$ can significantly increase the incidence of cardiac abnormalities in mice, chickens and zebrafish (15-17). Only 10-25% of the total cases of CHD have been demonstrated to be caused solely by genetic factors, with the majority of the cases being associated with external factors (18). Recent investigations by Yan *et al* (19) have summarized five primary mechanisms through which $PM_{2.5}$ affects adverse birth outcomes: Transcriptional and translational regulation, oxidative stress (OS) and inflammatory responses, and epigenetic regulation. While the present study review provides valuable insights into the broader developmental toxicity of $PM_{2.5}$, it offers a limited focus on the specific cardiac effects. Feng *et al* (20) systematically reviewed the molecular and pathophysiological mechanisms by which $PM_{2.5}$ impacts the cardiovascular system, encompassing metabolic activation, OS, genetic toxicity, inflammation, Ca^{2+} dysregulation, autophagy interference and apoptosis induction. Additionally, Liang *et al* (21) proposed an adverse outcome pathway framework to elucidate the relationship between $PM_{2.5}$-induced molecular events and adverse cardiac outcomes, suggesting that excessive reactive oxygen species (ROS) generation and activation of aromatic hydrocarbon receptors (AhR) are critical initiating events (21). These events lead to OS, endoplasmic reticulum stress (ERS), DNA damage, inflammation and activation of the Wnt/β-catenin pathway, ultimately resulting in apoptosis and impaired cardiomyocyte differentiation.

Despite significant advances in understanding $PM_{2.5}$'s cardiac developmental toxicity, there remains a notable deficiency in research focusing on the specific components of $PM_{2.5}$ that drive these detrimental effects. The mechanisms through which gestational exposure to $PM_{2.5}$ induces cardiac developmental toxicity require further elucidation, and our current understanding remains limited. Therefore, it is essential to explore strategies for preventing and controlling $PM_{2.5}$ exposure and to investigate the underlying mechanisms of its cardiac developmental toxicity. The present review aimed to highlight the need for further research on the specific components of $PM_{2.5}$ that drive cardiac developmental toxicity. These mechanisms were detailed and the sources and components of $PM_{2.5}$ were linked with their corresponding pathways of action, enhancing the understanding of $PM_{2.5}$-induced cardiac developmental toxicity. Finally, mitigation strategies to reduce health risks associated with $PM_{2.5}$ exposure were discussed and future perspectives on these strategies were outlined.

2. Cardiac developmental toxicity of $PM_{2.5}$

Previous epidemiological studies on the association between $PM_{2.5}$ exposure and CHD have yielded inconsistent conclusions (12,22-26), probably due to the heterogeneities of the studies concerned. Existing evidence suggests that the association between $PM_{2.5}$ and CHD is mainly focused on pregnant women exposed to $PM_{2.5}$ between the second and seventh week of pregnancy, a critical period for cardiac development (27). Furthermore, pro-gestational exposure to $PM_{2.5}$ is also detrimental for pregnant women and infants (28). It is worth noting that maternal exposure to $PM_{2.5}$ increases the risk of CHD in offspring, with the most susceptible time windows being 7-12 weeks before pregnancy and 3-9 weeks after pregnancy, demonstrating the especially adverse effects of $PM_{2.5}$ exposure on the risk of developing CHD with respect to cardiac development during these two critical periods (29). Several studies that have explored the association between gestational $PM_{2.5}$ exposure and CHD subtypes are presented in Table I.

3. Potential mechanisms underlying the cardiac developmental toxicity of $PM_{2.5}$

Interference with genes associated with cardiac development. As transcription factors, GATA4 and NKX2.5 perform crucial roles in fetal cardiac development. Gestational $PM_{2.5}$ exposure may increase the risk of GATA4 and NKX2.5 mutations, directly causing fetal cardiac abnormalities. Wu *et al* (30) found that gestational $PM_{2.5}$ exposure leads to cardiac hypertrophy with elevated mRNA levels of GATA4 in offspring mice. Moreover, the important regulatory role of GATA4 in signaling pathways involved in cardiac development has been confirmed (31,32). It has been revealed to regulate the expression of key downstream genes involved in cardiac cell proliferation, development and hypertrophy, including ANP, CARP, a-MHC and β-MHC (32).

As a key factor in myocardial formation, the downregulation of GATA4 leads to an increase in the risk of cardiac structural abnormalities and cardiovascular malformations in the fetus. Inhibition of GATA4 in the early stage of cardiac development has been revealed to be associated with myocardial hypoplasia and CHD, whereas its inactivation in the late stage of cardiac development leads to decreased cardiac function (32). GATA4 is involved in normal cardiac development, functional gene expression, and the pathological processes of cardiac hypertrophy. It has been recognized as a key effector mediating cardiac gene transcription in response to hypertrophic stimuli. In addition, during myocardial hypertrophy, GATA4 serves as a molecular 'bridge' connecting multiple nuclear factors, including myocyte enhancer factor 2C (Mef2c), Nkx2.5 and AP1 (33,34).

Dysfunction of genes associated with heart function. In addition to the importance of the concentration of $PM_{2.5}$, specific chemical components therein may exert more critical and important roles in the negative effects on health (35). Although heavy metals and PAHs only account for a small proportion of the $PM_{2.5}$ mass, their potential toxicity should not be underestimated. $PM_{2.5}$ exposure elicits stronger effects on the expression of cardiac genes than it does on genes in the

Table I. Associations between $PM_{2.5}$ exposure and congenital heart defects subtypes.

First author, year	CHD subtype	Case number	Exposure period	Adjusted OR (95% CI)	(Refs.)
Yang *et al*, 2021	VSD	2131	First trimester	0.98 (0.89-1.09)	(255)
Agay-Shay *et al*, 2013		493	Continuous exposures	0.88 (0.77-1.02)	(22)
Schembari *et al*, 2014		106	Weeks 3-8 of pregnancy	0.49 (0.28-0.89)	(25)
Girguis *et al*, 2016		864	Weeks 3-7 of pregnancy	1.08 (0.86-1.37)	(23)
Huang *et al*, 2019		218	Weeks 3-8 of pregnancy	1.15 (0.94-1.40)	(12)
Lavigne *et al*, 2019		326	Weeks 2-8 of pregnancy	1.99 (1.04-3.82)	(24)
Yang *et al*, 2021	ASD	1475	First trimester	0.82 (0.73-0.92)	(255)
Agay-Shay *et al*, 2013		534	Continuous exposures	0.95 (0.89-1.01)	(22)
Girguis *et al*, 2016		864	weeks 3-7 of pregnancy	1.09 (0.86-1.37)	(23)
Huang *et al*, 2019		147	Weeks 3-8 of pregnancy	1.31 (1.01-1.69)	(12)
Lavigne *et al*, 2019		581	Weeks 2-8 of pregnancy	1.49 (0.93-2.39)	(24)
Yang *et al*, 2021	TGA	284	First trimester	1.32 (1.02-1.70)	(255)
	ToF	209	First trimester	1.04 (0.77-1.39)	
Girguis *et al*, 2016		153	Weeks 3-7 of pregnancy	1.00 (1.59-1.71)	(23)
Huang *et al*, 2019		123	Weeks 3-8 of pregnancy	1.11 (0.85-1.45)	(12)
Yang *et al*, 2021	vPS	171	First trimester	0.83 (0.60-1.14)	(255)
	AVSD	136		1.19 (0.82-1.72)	
	DORV	121		2.14 (1.43-3.22)	

VSD, ventricular septal defect; ASD, atrial septal defect; TGA, d-transposition of the great arteries; ToF, tetralogy of Fallot; vPS, valvular pulmonary stenosis; AVSD, atrioventricular septal defect; DORV, double outlet right ventricle; CHD, congenital heart defect.

lung, especially those genes associated with collagen, laminin and calcium (Ca^{2+}) signaling (36). $PM_{2.5}$ exposure leads to elevated levels of several genes associated with collagen deposition, including collagen type I, α1, Col3α1 and transforming growth factor β1 (TGFβ1) (37). Cardiac fibrosis is associated with an imbalance between the generation and degradation of extracellular matrix, resulting in the accumulation of scar tissue; consequently, $PM_{2.5}$-induced cardiac fibrosis reduce the compliance of the extracellular matrix, impairing the cardiac capability to contract and relax normally. Qi *et al* (38) reported that $PM_{2.5}$ and its water-soluble components associated with transportation induce cardiomyocytes dysfunction through ERS and autophagy. In this regard, heavy metals and PAHs in $PM_{2.5}$ may be the primary influencing factors (38). In addition, the impact of $PM_{2.5}$ exposure on cardiac function has been revealed to be seasonal, as levels of locally sourced elements in $PM_{2.5}$ demonstrate significant seasonal changes (39). In summer, the emissions of iron (Fe), lead (Pb) and zinc (Zn) from steel plants, as well as Fe, titanium (Ti), chromium (Cr), manganese (Mn) and arsenic (As) from automobiles, have been revealed to be significantly associated with a reduction of the standard deviation of the mean to mean intervals (36). By contrast, in winter, elements such as barium (Ba), Zn, As and rubidium (Rb) were revealed to be correlated with an increased heart rate (39). Moreover, an association between an increased heart rate, albeit with decreased heart rate variability, was observed with nickel (Ni) and element carbon (40,41).

Ca^{2+} ions act as an important mediator in maintaining the normal contraction and relaxation of the heart, and numerous studies have identified calmodulin as an important target for cardiac dysfunction. After uterine exposure to $PM_{2.5}$, significant changes in the levels of Ca^{2+}-regulatory proteins, including sarcoplasmic/endoplasmic reticulum Ca^{2+}-ATPase 2A (SERCA2A), sodium (Na^{+})/Ca^{2+} exchanger (NCX) and the voltage-gated Ca^{2+} channel (Cav1.2), were observed in fetal mice hearts on day 14 following pregnancy (42). Newborn mice exposed to $PM_{2.5}$ during pregnancy experience cardiac dysfunction due to changes in Ca^{2+}-processing proteins that are associated with downregulated levels of NCX and CaV1.2 in the heart. Furthermore, in a study on heart failure in rabbits, inhibition of NCX led to a reduction in the burden of premature ventricular beats, although there was no resultant inhibition of secondary Ca^{2+} elevation. As a compensatory mechanism, the levels of Serca2A and phosphorylated phospholamban were found to increase to cope with higher intracellular Ca^{2+} concentrations. The cardiac action potential performs a crucial role in cardiac synchronization, as it is regulated by cardiac ion channels such as voltage-gated Na^{+} and potassium (K^{+}) channels (43). Park *et al* (44) found that exposure to particulate matters induced the abnormal expression (downregulation) of fetal heart ion channel-associated genes, including scn5lab, kcnq1 and kcnq1.

OS. OS, caused by free radicals, serves as a key factor leading to cellular and tissue oxidative damage, as well as being a major driver of aging and various diseases. ROS are the most important free radical that cause oxidative damage to the body. OS is the most common mechanism underlying $PM_{2.5}$-induced damage (45,46). Transition metals [Fe, Cu and Mn] and organic compounds from $PM_{2.5}$ are able to induce the production of ROS and reactive nitrogen species (RNS), and the ability of $PM_{2.5}$ to induce ROS has been significantly

correlated with the concentrations of PAHs and specific transition metals therein (47). $PM_{2.5}$ may induce OS in target cells through a variety of pathways. First, $PM_{2.5}$ contains persistent free radicals that are found in the environment, especially combustion-derived particles (48). Secondly, numerous organic compounds from $PM_{2.5}$ can be metabolized into reactive electrophilic metabolites, which thereby induce the further generation of ROS (49). Thirdly, transition metals can induce ROS through the Fenton reaction (50). Finally, OS may also be caused by the $PM_{2.5}$-mediated activation of inflammatory cells, which are able to produce both ROS and RNS (51). On the other hand, $PM_{2.5}$ may also decrease the cellular antioxidant capacity through downregulating the expression of antioxidant enzymes, such as superoxide dismutase and glutathione metabolizing enzymes (52). ROS react with biomolecules such as proteins and DNA, resulting in various adverse effects on cells, including the disruption of their structure and function, which ultimately leads to damage to target cells and tissues. Two pathways are mainly involved in the pathogenic mechanisms underlying: One is gene damage resulting from genetic mutations, and the other is damage that is caused to the cell membrane, which results in changes in its permeability through lipid peroxidation, leading to physiological changes such as inflammation.

The embryonic development of both humans and zebrafish is abnormally sensitive to OS induced by ROS, and excessive ROS production is considered one of the factors contributing to CHD (53,54). Ren *et al* (55) demonstrated that extractable organic matter (EOM) from $PM_{2.5}$ is able to induce ROS production, thereby increasing the levels of nuclear factor erythroid 2-related factor 2 (Nrf2) signaling pathway-associated genes [namely, SOD2, glutathione S-transferase (GST) P1/2, catalase (CAT) and heme oxygenase-1 (HO-1)], with the Nrf2 signaling pathway being the major pathway that is activated by OS. 2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD), an AhR agonist, was revealed to cause an upregulation of the protein levels and activity of Nrf2 in mice (56). The presence of multiple AhR-binding elements located in the promoter and first intron of Nrf2a and Nrf2b suggests that AhR exerts a regulatory role with respect to their transcription (57). According to other research results, OS, in turn, may inhibit the activity of AhR (58). Elbekai and El-Kadi (59) reported that the ROS scavenger N-acetylcysteine (NAC) could ameliorate the inhibitory effects of chromium on AhR activity in human liver cell line (59). NAC treatment led to an increase in the activity of cytochrome P450, family 1, subfamily A, polypeptide 1 (Cyp1a1), whereas the inhibitory effects of AhR inhibitor, CH223191, were alleviated (60). However, Ren *et al* (55) found that NAC did not reduce EOM-induced AhR activity, suggesting that the effects of OS on the AhR signaling pathway may be species- or cell type-specific (55). Zebrafish possess two Nrf2 genes (Nrf2a and Nrf2b), whose downstream genes (SOD2, GSTP1/2, CAT and HO-1) exert a range of antioxidant effects, and this may represent a negative feedback mechanism to circumvent EOM-induced excessive ROS (57).

AhR are activated by PAHs from $PM_{2.5}$, which consequently upregulates the levels of CYP metabolic enzymes and induces ROS via superoxide/hydrogen peroxide (61-63). Vertebrate embryos are highly susceptible to OS due to their limited antioxidant capacity (54). Ren *et al* (55) demonstrated that CH223191 and NAC are able to markedly alleviate $PM_{2.5}$-induced zebrafish embryonic cardiac abnormalities. Furthermore, the two compounds were also revealed to reduce EOM-induced ROS generation, DNA damage and cell apoptosis, ameliorating the resultant changes in the mRNA expression levels of genes associated with cardiac development (NKX2.5 and SOX9B), OS (NRF2A, NRF2B, GSTP1, GSTP 2, SOD2, HO-1 and CAT) and apoptosis (p53 and Bax). These results confirmed that AhR mediates EOM-induced OS, leading to DNA damage and cell apoptosis, thereby promoting the cardiac developmental toxicity of $PM_{2.5}$ (55). The most significant OS response induced by $PM_{2.5}$ exposure is excessive oxidative phosphorylation in myocardial cells, which ultimately leads to mitochondrial damage and myocardial cell death (64). It is noteworthy that such adverse effects may often be significantly alleviated by antioxidants (65), demonstrating the potential of antioxidants in either preventing or mitigating OS damage caused by $PM_{2.5}$ exposure.

Inflammation. Inflammation is an adaptive response for the body that both enables the clearance of harmful stimuli and heals damaged tissues. However, persistent or chronic inflammation may be detrimental to the body (66). As an important mechanism that is associated with $PM_{2.5}$ toxicity, the inflammatory response may impose the negative effects of $PM_{2.5}$ on the cardiovascular, pulmonary and nervous systems (67). The PAHs, metals, water-soluble ions as well as various bioactive substances (such as endotoxins) that are contained in $PM_{2.5}$ may cause inflammation, a process that is associated with the polarization of pro-inflammatory macrophages (68). $PM_{2.5}$ has been revealed to cause an increase in the levels of ROS in macrophages, and is recognized by the Toll-like receptors TLR4 and TLR2, leading to the induction or exacerbation of acute inflammation and thereby promoting M1 polarization of macrophages (69). This process may also involve the activation of Notch signaling due to a decreased level of the microRNA, miR-34a-5p (70). In addition, exposure to PAHs has been revealed to upregulate the levels of inducible nitric oxide synthase (iNOS), NLR family pyrin domain containing 3 (NLRP3) and tissue protease B in macrophages, demonstrating that pyroptosis provides the basis for the pro-inflammatory polarization of macrophages induced by exposure to PAHs (71). Myocardial macrophages are able to eliminate the defective mitochondria that are released by cardiomyocytes, thereby maintaining cardiac mitochondrial homeostasis. However, in the absence of membrane-bound bone marrow epithelial reproductive receptor tyrosine kinase (MerTK), myocardial macrophages lose the ability to capture and eliminate defective mitochondria, leading to dysfunctional cardiac metabolism and left ventricular dysfunction, suggesting that MerTK fulfills a crucial role in supporting cardiac homeostasis (72). Pro-inflammatory polarization of myocardial macrophages promotes the lysis of MerTK, which affects the ability of myocardial macrophages to participate in cardiac repair, consequently leading to cardiac homeostasis imbalance, myocardial injury and decreased cardiac function.

The important pro-inflammatory cytokines tumor necrosis factor (TNF)-α and interleukin (IL)-6 are involved in the pathogenesis of heart failure, cardiac hypertrophy and

fibrosis (73,74). It has been revealed that exposure to $PM_{2.5}$ in the uterus induces the expression of pro-inflammatory cytokines in the hearts of the offspring mice, leading to cardiac inflammation (30,42). Li *et al* (75) through studying the cardiac inflammatory response, demonstrated that the levels of TNF-α and IL-1β were significantly increased in offspring mice subjected to uterine $PM_{2.5}$ exposure. Long-term exposure to $PM_{2.5}$ was revealed to cause a marked upregulation of the levels of intercellular adhesion molecule-1 (ICAM-1) and C-reactive protein in rat myocardial tissues, leading to ultrastructural changes in myocardial cells and inflammatory cell influx (76). Among the signaling molecules that regulate the inflammatory response, nuclear factor-κB (NF-κB) is the major signaling molecule that is involved in the production of cytokines, chemokines and growth factors, regulating the expression of immune and inflammatory response-associated genes (77). The NF-κB signaling pathway, involved in tissue damage, has been reported to have a role in systemic inflammation induced by $PM_{2.5}$ (78). Inflammation fulfills crucial roles in systemic myocardial hypertrophy and cardiotoxicity induced by particulate matter (79). Jiao *et al* (80) found that the $PM_{2.5}$-mediated induction of inflammation is dependent on the activation of the key transcription factor NF-κB, which enhances the expression of the downstream factors, TNF-α and IL-1β. Exposure to $PM_{2.5}$ *in vivo* has been revealed to activate the NF-κB signaling pathway, leading to inflammatory responses in target tissues and organs (81). Interesting, the activation of NF-κB, with the subsequent inflammatory response that is caused by exposure to $PM_{2.5}$, may be suppressed by antioxidants, suggesting the involvement of ROS and/or RNS in $PM_{2.5}$-mediated NF-κB activation (52). Considering that NF-κB also triggers the generation of ROS and nitric oxide (NO), this may form a positive feedback loop that amplifies downstream responses upon $PM_{2.5}$ exposure (82). An increased level of OS resulting from exposure to $PM_{2.5}$, in turn, mediates the activation of downstream inflammatory signaling pathways, including the mitogen-activated protein kinase (MAPK), c-Jun N-terminal kinase (JNK)/p53, Nrf2/NLRP3, TLR/MyD88 and extracellular signal-regulated kinase (ERK)/AKT pathways (83). $PM_{2.5}$ has been revealed to increase the protein level of cleaved IL-1β, a key downstream factor for NLRP3 inflammasome activation, further confirming that $PM_{2.5}$ can activate the NLRP3 inflammasome in myocardial tissue; NLRP3 inflammasome activation, in itself, has a potential role in mediating the pathological damage resulting from $PM_{2.5}$ exposure in the mouse heart (84). The augmented levels of ROS triggered by exposure to $PM_{2.5}$ may activate the MAPK and NF-κB pathways, thereby increasing the synthesis of inflammatory proteins and leading to changes in membrane permeability and mitochondrial dysfunction (85). It is worth noting that mitochondrial DNA (mtDNA) lacks the ability to repair DNA, making it more susceptible to oxidative damage compared with nuclear DNA. Mitochondrial dysfunction and subsequent cell death can trigger inflammation in various types of tissues (86). Mitochondrial dysfunction makes a key contribution to the $PM_{2.5}$-mediated inflammatory response (87). mtDNA and n-formyl peptides that are released from dysfunctional mitochondria both trigger inflammation. $PM_{2.5}$ exposure has also been revealed to increase the expression and release of adhesion molecules, including E-selectin, P-selectin and ICAM-1, leading to monocyte/macrophage adhesion (88), whereas, on the other hand, diminishing the levels of circulating endothelial progenitor cells that are involved in postnatal endothelial repair and regeneration (89), thereby exacerbating the inflammatory response. Inflammatory factors such as cyclooxygenase-2 (COX-2) are able to inhibit the activity of Ca^{2+} pumps in the endoplasmic reticulum, thereby inducing ERS through upregulating iNOS expression (90), suggesting that inflammation induced by $PM_{2.5}$ can trigger ERS. Furthermore, $PM_{2.5}$ has been revealed to activate the unfolded protein response (UPR), which provides an additional mechanism for triggering ERS (91). UPR signaling both stimulates the expression of inflammatory cytokines and induces the activation of NF-κB (92), suggesting that UPR signaling makes an important contribution towards $PM_{2.5}$-induced ERS in the inflammatory process, and that this serves as an inflammatory factor both as a cause and as a consequence of ERS (93). Ca^{2+} leakage from the endoplasmic reticulum directly drives the production of mitochondrial ROS (mtROS), affecting downstream signaling pathways and rendering cells more susceptible to autophagy (94). It is now well documented that inflammation, ERS and autophagy are closely interlinked, and that these processes can interact with each other. Taken together, these aforementioned findings suggest that the cardiac developmental toxicity that is caused by $PM_{2.5}$ is associated with inflammation, ERS and autophagy.

Mitochondrial impairment. The biogenesis and functional improvement of mitochondria are crucial processes for enabling the differentiation and maturation of the heart (95). Previously, investigations of the molecular mechanisms associated with mitochondria underlying the toxic effects of environmental pollution have been mainly focused on the mitochondrial permeability transition pore (mPTP), mitochondrial dynamics, mtDNA function and the mitochondrial respiratory chain system, along with mitochondrial damage-associated signaling pathways. $PM_{2.5}$ was found to induce mitochondrial impairment in exposed individuals (96), and mitochondrial dysfunction has been revealed to mediate the cardiovascular damage caused by $PM_{2.5}$ to a certain extent (97). Enhancing the production of cardiac energy may be achieved through growing the mitochondria count (98), and swelling, disrupted crista and mitochondrial vacuolization represent the primary manifestations for cardiac mitochondrial pathological changes (99). Acute exposure to PM can lead to significant mitochondrial dysfunction, accompanied by decreased cardiac oxygen consumption, succinate dehydrogenase activity and mitochondrial membrane potential, as well as impaired oxidative phosphorylation (100). These findings suggested that mitochondrial damage caused by $PM_{2.5}$ exposure may have a bearing on mitochondrial dysfunction.

Inflammatory response and OS, fulfilling important roles in $PM_{2.5}$-induced cardiac injury, can produce a large number of free radicals that are closely associated with mitochondrial damage (101). Proteins or complexes modulating cell apoptosis are only able to function via cytochrome c after entering the mitochondrial membrane (102). Therefore, mitochondria exert a crucial role in the cardiac toxicity that is mediated by $PM_{2.5}$. In order to exert their own function, mitochondria must undergo continuous fission and fusion, abnormalities of which

may induce diseases (103). OPA1 mitochondrial dynamin-like GTPase (OPA1) along with Mfp-1 and -2 jointly regulate mitochondrial fusion, with the large GTPase, dynamin-related protein 1 (Drp1) and the mitochondrial outer membrane protein adaptor, fission 1 (Fis1) mediating mitochondrial fission (104). The normal expression of fusion/fission genes is a prerequisite for the normal function of mitochondria, otherwise mitochondrial dysfunction may occur (105). Wang *et al* (16) identified elevated levels of OPA1, Mfn1, Drp1 and Fis1 in offspring rats with the dosage of gestational $PM_{2.5}$ exposure, and surmised that the dysregulated mitochondrial fusion/fission genes resulting from gestation $PM_{2.5}$ exposure in these rats would exert detrimental effects on mitochondrial damage, subsequently leading to an induction of cardiac developmental toxicity in the offspring.

OS, an imbalance of Ca^{2+} homeostasis, and inflammation are all closely associated with mitochondrial dysfunction in various heart diseases (106). First, mitochondria are the main source of ROS production (107). Excessive ROS has been revealed to induce lipid peroxidation, thereby leading to mitochondrial permeability, decreased membrane potential and mitochondrial swelling (108). In addition, mitochondrial superoxide reacts with RNS such as NO to form peroxynitrite, further damaging mitochondrial structure and function (109); therefore, mitochondria are sensitive targets for $PM_{2.5}$ and OS (110). Rodriguez-Enriquez *et al* (111) reported that ROS, Ca^{2+} overload, decreased mitochondrial membrane potential and excessive mitochondrial permeability are key triggers of mitochondrial swelling and outer membrane rupture. A strong correlation was found to exist between mitochondrial dysfunction and the severity of inflammation (112). It is well established that peroxisome proliferator-activated receptor-γ coactivator 1α (PGC-1α) is the main mediator for mitochondrial biogenesis and function in mammals (113), and environmental chemicals have been revealed to induce mitochondrial damage via inhibiting PGC-1α (114). Chen *et al* (115) reported that AhR activated by $PM_{2.5}$ directly inhibits sirtuin 1, thereby both reducing the levels of PGC-1α and increasing its level of acetylation, which has the effect of diminishing its activity. Damaged PGC-1α subsequently induces mitochondrial dysfunction, ultimately leading to cardiac developmental defects in zebrafish juveniles (115). In addition, this research group also found that EOM derived from $PM_{2.5}$ induces the overexpression of CYP1A1 via activating AhR, leading to the generation of mtROS. The increase in mtROS levels subsequently exacerbates the opening of the mPTP, which, in turn, promotes the accumulation of mtROS. Opening of the mPTP promotes the release of pro-apoptotic substances, thereby triggering the intrinsic apoptotic pathway and leading to cardiac defects (116). Further investigations are required, however, regarding the possible involvement of other associated mechanisms of mitochondrial dysfunction elicited by $PM_{2.5}$, such as cytochrome c release, mtDNA changes and cell apoptosis, along with mitochondrial genomic variations in $PM_{2.5}$-induced cardiac developmental toxicity.

Epigenetic modification. Epigenetic modifications, including DNA methylation (DNAm), histone modifications and RNA-mediated processes, are sensitive to environmental stress and are considered to serve as a 'bridge' between environmental and genetic factors by certain researchers (117,118). Epigenetic modifications fulfill an important role in cardiac development and the occurrence of various diseases, with DNAm as the primary form, which can be inherited and reversed. To date, however, little is known regarding the underlying molecular mechanisms through which $PM_{2.5}$ triggers the epigenetic changes that lead to cardiac developmental toxicity.

1 N^6-Methyladenosine (M6A) RNA methylation. M6A RNA methylation, as the most common form of RNA modification, accounts for ~60% of the total number of RNA modifications. M6A RNA methylation, a dynamic and reversible process, occurs under the regulation of methyltransferases (including METTL3 and METTL14), demethylases (such as FTO and ALKBH5,), and binding proteins (including YTHDF1/2/3 and ythdc2/2) (119). M6A RNA methylation regulates gene expression through affecting mRNA stability, selective splicing, nuclear output and protein translation (120,121). M6A RNA methylation has been reported to be involved in excessive cellular ROS production and apoptosis (122-124). A crucial role of m6A modification in heart development has been demonstrated (124,125), and $PM_{2.5}$ has been revealed to induce changes in m6A RNA methylation in rats and mice (126,127). Ji *et al* (128) found that EOM from $PM_{2.5}$ caused a significant inhibition of m6A RNA methylation levels in zebrafish juvenile hearts mediated via the AhR, although this inhibitory effect was restored by supplementation with betaine (the predominant methyl donor in the carbon metabolism cycle). Betaine can also mitigate EOM-induced ROS generation, cell apoptosis and cardiac defects, suggesting that EOM inhibits m6A RNA methylation by interfering with mettl14/mettl3 expression, leading to cardiac defects (128). These findings validated the hypothesis that m6A modification fulfills an important role in cardiac developmental toxicity induced by $PM_{2.5}$ exposure, although the antioxidant activity of betaine should not be overlooked. On the other hand, other studies have revealed that exposure to $PM_{2.5}$ leads to an upregulation of the levels of Mettl3 and total m6A methylation in mice lung tissues (127,129). The differences noted in the expression levels of m6A methyltransferase may be due to the differential responses of these genes to $PM_{2.5}$ exposure in embryonic/larval and adult tissues (130); another possibility is that changes in the level of m6A RNA methylation induced by $PM_{2.5}$ exposure may be due to species specificity.

Supplementing the diet with AhR inhibitor, CH223191, has been reported to successfully circumvent the occurrence of EOM-induced cardiac defects in zebrafish juveniles (17,55). Either adding betaine or overexpressing mett13/14 was revealed to ameliorate the effects of EOM-induced intracellular and mtROS, as well as reducing the level of apoptosis in zebrafish juvenile cardiomyocytes. Therefore, changes that occur in the level of m6A RNA methylation may be an important underlying cause of EOM-induced cardiac abnormalities. M6A modification has been revealed to regulate OS and cell apoptosis via regulating the expression of m6A-modified genes (131,132). Cao *et al* (133) reported that exposure to $PM_{2.5}$ increases ROS generation and apoptosis in rat cardiomyocytes, leading to cardiac injury. In addition, EOM from $PM_{2.5}$ led to OS-mediated cell apoptosis in zebrafish juvenile hearts (55). Collectively, these studies have demonstrated that gestational

exposure to $PM_{2.5}$ may cause OS and cell apoptosis through altering m6A modification, thereby causing cardiac developmental toxicity.

DNAm. DNAm, one of the most extensively studied epigenetic modifications, performs a crucial role in cardiac development. Abnormal DNAm has been revealed to be associated with the pathogenesis of CHD (134), and it has been revealed that $PM_{2.5}$ causes abnormal changes in DNAm (135); therefore, it is possible that DNAm may be associated with the cardiac developmental toxicity that is induced by $PM_{2.5}$ exposure. As a major environmental sensor, AhR is able to bind and be activated by various environmental pollutants, including PAHs (136,137). Following activation, AhR is translocated from the cytoplasm to the nucleus, where it regulates the transcription of target genes by directly binding to exogenous xenobiotic response elements in the promoter regions (138). AhR activated by TCDD was revealed to regulate the expression of DNA methyltransferase in zebrafish juveniles (139). Jiang *et al* (140) also found that EOM from $PM_{2.5}$ was able to activate AhR, resulting in abnormal DNAm in the heart of zebrafish juveniles. Regarding the specific process of DNAm, $PM_{2.5}$ exposure caused an upregulation of the levels of DNA methyltransferase 1 (DNMT1) in the lungs of mice; however, the level of DNMT1 was found to be downregulated in zebrafish embryos (140,141). Trace elements such as As, Pb, cadmium (Cd) and mercury carried by $PM_{2.5}$ particles are capable of penetrating the placenta (142), and this phenomenon has been revealed to cause alterations in placental DNAm (143,144). Supplementing the diet with folate was revealed to alleviate EOM-induced DNAm changes, thereby protecting zebrafish embryos against the cardiac developmental toxicity of $PM_{2.5}$ (140); this probably occurred since folate can act as a methyl donor to affect the expression of DNAm-associated genes (145).

Exposure to air pollutants may alter epigenetic modifications such as DNAm, which, in turn, may affect inflammation, disease development and the risk of deterioration. Exposure to several air pollutants associated with transportation, including $PM_{2.5}$, black carbon, ozone, nitrogen oxides and PAHs, leads to a decrease in DNAm. This may be due to both the reduced expression of methionine adenosyl-transferase 1A and single carbon metabolism efficiency mediated by oxidative species, resulting in a scarcity of the methyl donor of S-adenosylmethionine that is required for establishing and maintaining DNAm (146). Goodson *et al* (147) found that *in utero* exposure to diesel exhaust (DE) induced a decreased level of DNAm in the first exon of GM6307, suggesting that DE can affect the developing heart by altering epigenetic patterns. The mechanism(s) through which $PM_{2.5}$ exposure leads to DNAm changes, however, have yet to be fully elucidated. It has been revealed that exposure to DE increases the production of ROS (148), which, in turn, interact with DNA, thereby oxidizing methyl-cytosine to hydroxymethyl-cytosine (HMC). HMC has been revealed to prevent the binding of methyl binding proteins (MBPs) to methylated cytosine (149), which prevents normal chromatin silencing from occurring at these sites. In addition, 8-oxoguanine produced by guanine oxidative damage was also found to inhibit the binding of MBPs, thereby hindering the silencing of chromatin regions (149).

$PM_{2.5}$ has also been revealed to disrupt DNAm profiles (150), probably resulting in an exacerbation of the oxidative and inflammatory responses following $PM_{2.5}$ exposure. $PM_{2.5}$ inhalation exerts acute effects on DNAm in the promoter regions of genes that are associated with mitochondrial function and oxidative metabolism (151). Although mitochondria possess their own genetic material that differs from nuclear DNA, the majority of mitochondrial proteins are encoded by the nuclear genome. Exposure to $PM_{2.5}$ has been revealed to cause a marked alteration in the DNAm of nuclear genes in the mitochondrial pathway, suggesting that mitochondria form the primary target of $PM_{2.5}$. DNAm is a modifiable biochemical process, and supplementing the diet with B vitamins to ensure that methylation takes place has become an attractive means of drug intervention to counteract the loss of DNAm of inflammatory genes caused by $PM_{2.5}$ (152). In addition, supplementing B vitamins may also minimize DNA hypermethylation to a great extent.

Histone acetylation modification. Histone acetylation modification is an important topic for epigenetic research. Unlike DNAm, the effects of histone modifications on gene expression may vary, depending on specific chemical modifications (153). Abnormal histone modifications associated with exposure to various environmental chemicals may lead to a large number of diseases, including cardiovascular diseases. For example, the histone modifications H3K9me2 and H3K9ac were revealed to be associated with As exposure, increasing the risk of several cardiovascular diseases (154). In addition, Zhang *et al* (155) demonstrated an association between the H3K36me3 modification and exposure to PAHs and DNA damage, suggesting that the involvement of specific histone modifications in PAHs results in an induction of DNA damage responses. The processes of histone acetylation and deacetylation are considered to provide an important regulatory mechanism for mediating cardiovascular development and myocardial injury. Histone deacetylation has been demonstrated to participate in the regulation of gene transcription under stress or pathological conditions (156). Histone acetylation has an important role in myocardial hypertrophy events that are induced by $PM_{2.5}$ exposure. Significantly increased protein levels of acetylated H3K9 were observed in the hearts of mice exposed to $PM_{2.5}$, which led to an upregulation of hypertrophic transcription factors (75). In summary, the imbalances between histone methylation and demethylation, as well as between acetylation and deacetylation, that are caused by $PM_{2.5}$ exposure are considered to increase the likelihood of cardiac dysplasia and cardiovascular system-associated diseases.

Among the histone acetyltransferases (HATs), p300 is closely associated with the transcriptional regulation of cardiac development (157). SIRT3, the third type of histone deacetylase, is able to inhibit the OS response and promote the tricarboxylic acid cycle, which has the effect of enhancing myocardial ATP energy supply and contraction, as well as regulating the energy metabolism balance (158). Knockout of SIRT3 was revealed to lead to myocardial mitochondrial dysfunction and cardiac dysfunction (159). Furthermore, the abnormal expression of HATs and HDAC led to imbalanced histone acetylation modifications, giving rise to cardiac developmental disorders (160). Exposure to $PM_{2.5}$ in the uterus is known to lead to cardiac

hypertrophy in adulthood. P300/CREB binding protein mediated histone acetylation modification may exert an important role in the upregulation of thickening transcription factors, such as GATA binding protein 4 (GATA4) and Mef2c. To date, the mechanism(s) of $PM_{2.5}$-induced histone modification are poorly understood. Environmental chemicals may directly alter histone methyltransferases or demethylases. For example, Ni exposure has been revealed to inhibit the activity of lysine-specific demethylase 3A by binding and substituting Fe^{2+} ions, thereby increasing H3K9me2 modification (161).

ERS. The endoplasmic reticulum performs a crucial role in terms of protein synthesis and folding, and post-translational modifications. The disruption of endoplasmic reticulum function may lead to accumulated unfolded or misfolded proteins in the lumen, which activates the UPR, a complex intracellular signaling pathway aimed at restoring protein balance. The endoplasmic reticulum is closely associated with normal development and homeostasis of the internal environment, and it has a crucial role in cardiac development and function (162). Zhu *et al* (163) found that Cd exposure increased ERS in myocardial tissue and primary cardiomyocytes, which was manifested in elevated levels of stress-associated genes. Impaired cardiac contractility and prolonged diastolic duration have been revealed to be common pathological features of the ERS-stimulated heart (164). Previous studies have also suggested that $PM_{2.5}$ is capable to induce ERS (165,166); however, the mechanism(s) underlying $PM_{2.5}$-induced ERS, and its role in cardiac development, has yet to be elucidated. EOM from $PM_{2.5}$ was revealed to induce AhR-mediated ROS production in zebrafish embryonic hearts (17,55,167). In addition, OS induces ERS through disrupting the normal processes of protein folding/transport and altering Ca^{2+} homeostasis (168-170). On the other hand, ERS was also demonstrated to increase the content of ROS, and to induce OS (171). Early-stage embryos are highly susceptible to oxidative damage, and excessive ROS is considered one of the causative agents for CHD (53,54); therefore, $PM_{2.5}$ may induce ERS through AhR-mediated ROS overproduction, thereby inducing cardiac developmental toxicity via oxidative damage.

Cardiac development is a coordinated process depending on the subtle balance among cell proliferation, apoptosis and differentiation. It is well established that long-term or severe ERS can lead to cell apoptosis, with C/EBP homologous protein (CHOP) being recognized as one of the most important mediators. The expression of CHOP may be upregulated through activating all three ERS sensors, namely: Activating transcription factor 6, protein kinase RNA like endoplasmic reticulum kinase and inositol requiring enzyme 1α. As a transcription factor, CHOP induces cell apoptosis through downregulating members of the antiapoptotic Bcl protein family and increasing the level of endoplasmic reticulum oxidoreductin 1α. EOM was reported to induce apoptosis of zebrafish embryonic cardiomyocytes, although the increased level of apoptosis was attenuated via inhibiting AhR activity or ROS production (55,172); furthermore, ERS was found to have a key role in this process.

Autophagy. Autophagy is crucial for heart development. Numerous autophagic defects are known to be associated with cardiovascular diseases, including atherosclerosis and cardiomyopathy (172). Autophagy has an important role in the process of cardiac remodeling, including the morphogenesis of cardiac tissues and their eventual differentiation into cardiomyocytes. Atg5-deficient mice were demonstrated to have abnormal heart valves and separated ventricular (173). In a zebrafish cardiac development model, knocking down the core autophagy genes resulted in various defects, including cardiac blood-flow defects and atrial enlargement, among other defects (174). In addition, knocking down these autophagy genes resulted in profound changes in the levels of developmental genes, including certain key transcription factors that are necessary for cardiac development. The knockdown of these genes also led to the accumulation of dead cells in the developing heart, demonstrating the necessity of autophagic clearance of dead cells for normal cardiac remodeling. Cardiac-specific Atg5 deficiency in adult mice was revealed to lead to mitochondrial aggregation and ventricular dilation, demonstrating the vital role that autophagy has in cardiac cell development and homeostasis (175).

As a common heavy metal adsorbed on $PM_{2.5}$, Cd has been revealed to induce autophagy through a variety of mechanisms, including the ROS-dependent signaling pathway. Cd can disrupt the electron transport chain in mitochondria, especially via binding to the Q0 site of cytochrome b on complex III, leading to an accumulation of semi-ubiquinone. As an unstable molecule that easily transfers electrons to molecular oxygen, semi-ubiquinone results in the formation of superoxide and OS (176). Secondly, there is the ERS pathway: Ca^{2+} is an important signaling molecule for ERS-induced autophagy (177). ERS leads to the release of Ca^{2+} from the endoplasmic reticulum into the cytoplasm (178), thereby activating various kinases that are involved in the autophagy signaling pathway, including mammalian target of rapamycin (mTOR) and AMP-activated protein kinase (177). Ca^{2+} on the outer surface of the endoplasmic reticulum membrane is closely associated with the initiation of autophagosome formation (179). Thirdly, there is the mTOR pathway: Cd activates the AKT/mTOR pathway, thus initiating autophagy, which thereby induces various diseases (180). Finally, there are the Beclin-1 and Bcl-2 family pathways: In the presence of Cd, the increased release of Ca^{2+} in the endoplasmic reticulum leads to a separation of Beclin-1 from Bcl-2, which thereby activates cellular autophagy (181).

As another cellular protective mechanism for UPR, autophagy contributes to the degradation of the accumulated unfolded or misfolded proteins in the endoplasmic reticulum, thereby restoring endoplasmic reticulum homeostasis and further improving the overall cell survival rate (182). However, autophagy is also a 'double-edged sword' since excessive autophagy may promote cell death through excessive self-digestion and the degradation of essential cellular components (183), thereby bringing about embryonic developmental toxicity (184). Autophagy exerts important roles in the processes of cellular and tissue balance, specialization, tissue differentiation and organogenesis (185); in addition, inflammation, ERS and autophagy are closely associated, and these processes have been revealed to interact with each other (186).

Apoptosis. As the principal means of cell death, apoptosis has an important role in maintaining cellular homeostasis.

Abnormal apoptosis can give rise to various diseases, including cardiovascular diseases. Apoptosis in mammalian cells is mainly triggered through two pathways: The endogenous (intrinsic) pathway initiated by mitochondria, and the exogenous (extrinsic) pathway initiated by death receptors. The former is controlled by the Bcl-2 family of proteins, whereas the latter involves members of the TNF family of proteins, with the resultant signaling cascade (187). Apoptosis induced by exposure to $PM_{2.5}$ has a participatory role in a series of signaling pathways, including the MAPK (133) and PI3K/Akt (188) pathways, with caspase-3 serving as a vital biomarker in this process (189). Yang *et al* (190) demonstrated that the mitochondria-mediated apoptosis pathway has a key role in the $PM_{2.5}$-induced toxicity of AC16 cardiomyocytes, leading to cardiac dysfunction. The mitochondrial pathway mainly activates caspase-9 by releasing cytochrome *c* into the cytoplasm, triggering downstream cascade reactions, and ultimately activating downstream caspase-3 (191). However, in zebrafish, 2,3-bromofluoranthene derived from PAHs is able to induce apoptosis of vascular endothelial cells and cardiac toxicity through both pathways simultaneously (192). In addition, dysregulation of cellular Ca^{2+} homeostasis may also lead to cardiomyocyte apoptosis. Ca^{2+} is one of the most important signal-transduction systems in cells, and a low intracellular Ca^{2+} concentration is a prerequisite for normal cellular function. After $PM_{2.5}$ has entered the circulatory system, it leads to an increase in the intracellular Ca^{2+} concentration, and an overload of Ca^{2+} will lead to DNA degradation, free radical production and protein kinase activation, ultimately leading to cell apoptosis (193).

Apoptosis can be induced by DNA damage and is crucial for normal cardiac development (194,195). Previous studies have suggested that excessive production of ROS during early embryonic development in zebrafish may lead to DNA damage and cell apoptosis (196-198). Ren *et al* (55) found that the levels of 8-hydroxydeoxyguanosine (8-OHdG) and cH2AX were raised in the embryonic hearts of zebrafish exposed to EOM, although these increases were significantly reduced in the presence of the ROS scavenger, NAC. This further demonstrated that NAC is able to attenuate EOM-induced apoptosis in zebrafish embryonic cardiomyocyte. Bcl2 binding component 3 (BBC3), a member of the Bcl-2 family, is an important participant in apoptosis (199). BBC3 is localized at the mitochondria under apoptotic stimulations, leading to mitochondria-mediated intrinsic cell apoptosis (200). Traf4a, a zebrafish homolog for human TNF receptor-associated factor 4, is also involved in the regulation of apoptosis (201,202). TRAF4 is also essential for development and can regulate ROS generation by stabilizing NADPH oxidase complexes (203). Knocking down BBC3 or TRAF4 leads to the termination of EOM-induced excessive ROS production and apoptosis in zebrafish embryonic hearts, suggesting that both genes are required for this process. Therefore, overexpression of these two genes may exacerbate cardiac abnormalities in zebrafish juveniles induced by EOM derived from $PM_{2.5}$.

However, it is necessary to further investigate whether other forms of cell death besides apoptosis and autophagic death, such as ferroptosis, may be associated with the cardiac developmental toxicity induced by $PM_{2.5}$ exposure, since $PM_{2.5}$ exposure results in excessive amount of ROS, and severely damaged mitochondria release large amount of Fe, thereby inducing ferroptosis.

AhR signaling. AhR, an essential ligand-activated transcription factor for the cytochrome P450 pathway, controls the expression of genes such as *CYP1A1*, *CYP1B1* and *CYP1A2* in the cytochrome P450 family (204). AhR can be activated by numerous environmental pollutants, including $PM_{2.5}$ (55). Following activation, AhR is dissociated from binding its ligands and enters the nucleus, forming a dimer with AhR nuclear transport protein, subsequently binding with enhancers to form heterologous reaction elements that are involved in the regulation of the expression of cytochrome P450 family genes. Employing the P19 cell line as an *in vitro* model, Chen *et al* (167) found that exposure to EOM derived from $PM_{2.5}$ for 2 days led to an inhibition of cardiac differentiation for the next 14 days, demonstrating the persistent adverse effects of $PM_{2.5}$ on cardiac development. Mechanistically, AhR mediates the inhibitory effects of EOM on P19 cell cardiac differentiation, probably through dysregulation of cell proliferation, altering the normal processes of Wnt signaling, and inducing breaks of DNA double strands.

It has been revealed that EOM derived from $PM_{2.5}$ activates the AhR signaling pathway, leading to cardiac abnormalities in zebrafish embryos (17,205). AhR performs an essential role in the cardiac development of fish, mammals, and other organisms. Activation of AhR can impair the cardiac differentiation of human embryonic stem cells (ESCs) (206-208). Considering that PAHs [such as BaK and benzo(a)pyrene] in EOM are strong AhR agonists, and that AhR signaling is activated following exposure to EOM, it may be inferred that AhR mediates EOM-induced cardiac developmental toxicity. The AhR repressor (AhRR) forms a negative feedback loop with AhR (209). Two types of AhRR analogs (Ahrra and Ahrrb) exist in zebrafish, and knocking down Ahrrb (but not Ahrra) was revealed to enhance the inducive effects of the AhR agonist TCDD on the CYP1 superfamily genes (210). Therefore, the AhR inhibitor, CH223191, may inhibit the AhR signaling pathway by inducing Ahrrb expression. In EOM-treated zebrafish, the mRNA levels of the most important AhR subtype, Ahr2, were found to remain unchanged, suggesting that the EOM activation of AhR may be based on conformational changes, rather than on mRNA level changes (211).

As a typical type of PAHs, exposure to TCDD impairs the cardiac differentiation of ESCs, and this impairment is mainly mediated by AhR. The generation of cardiomyocytes was most significantly inhibited in the case of human ESCs (and not mouse ESCs) exposed to TCDD during the ESC stage. By contrast, in the absence of TCDD, AhR is significantly inhibited in mouse ESCs, which decreases the expression of numerous pluripotent genes (212). In addition, ESC cardiac differentiation was found to be suppressed by TCDD exposure during embryonic formation via disrupting activin, bone morphogenetic protein and the Wnt signaling pathway, and through altering the expression of homologous cassette transcription factors (213-216). These differences suggest that human and mouse ESCs exhibit different susceptibility to TCDD toxicity, possibly due to species-specific differential expression patterns of AhR and its cofactors (217). Furthermore, AHR may regulate differential

target genes in different species or cells (218,219). Therefore, similarly to TCDD, $PM_{2.5}$ can inhibit the activation of mesodermal genes through AhR binding, interfering with the differentiation and development of normal cells, and thereby inhibiting mesodermal differentiation. Jiang *et al* (220) also found that $PM_{2.5}$ can activate the PI3K/akt2/mammalian target of rapamycin complex 1 signaling pathway through AhR/ROS induced PTEN inhibition, leading to activation of the mitochondria-mediated intrinsic apoptotic pathway and Wnt signaling inhibition, resulting in heart defects in zebrafish juveniles. It has been documented that folate supplementation during pregnancy helps to resist $PM_{2.5}$-induced cardiac developmental toxicity via targeting the AhR and Wnt/β catenin signaling pathways (205). This provides theoretical support for alleviating $PM_{2.5}$-induced cardiac developmental toxicity.

Wnt signaling. The Wnt/β-catenin signaling pathway has an essential role in the cardiac development of vertebrates (221), and its activation may induce cardiac specification in the early developmental stages, although this may be suppressed later (221). As a core transcription factor of the typical Wnt signaling pathway, β-catenin is able to regulate the expression of key genes in cardiac development (222). Chen *et al* (167) found that the mRNA and protein levels of β-catenin were downregulated in cells exposed to EOM derived from $PM_{2.5}$, suggesting a role of Wnt signaling in EOM-exerted cardiotoxic effects. It is well established that crosstalk exists between the AhR and Wnt/β-catenin signaling pathways (223,224), since activated AhR can antagonize β-catenin in colon cancer cells and zebrafish embryos (224). The Wnt/b-catenin signaling pathway has also been revealed to be crucial for embryonic cardiac development. In the absence of Wnt, cytoplasmic β-catenin is phosphorylated and degraded by a disruption complex composed of adenomatosis polysaccharide coli, Axin and glycogen synthase kinase-3β. Upon Wnt stimulation, cytoplasmic β-catenin is translocated into the nucleus, where it activates the transcription of genes essential for cardiac specification, such as Nkx2.5 and Sox9 (224-226). CH223191 and the Wnt/β-catenin activator, CHIR, were found to rescue the most of the EOM-induced cardiac defects, suggesting the involvement of the AhR and Wnt/β-catenin signaling pathways in cardiac developmental toxicity resulting from $PM_{2.5}$ exposure, and therefore the feasibility of employing AhR or Wnt/β-catenin antagonists to prevent the cardiac developmental toxicity from occurring (17). The typical Wnt/β-catenin signaling pathway regulates multiple steps in cardiac differentiation (167). The activation of Wnt signaling is crucial for both the formation of the mesoderm in the early stage of development as well as the morphogenesis of cardiac valve formation in later ones (227). Previous studies have demonstrated the inhibition of Wnt signaling by EOM in the embryonic heart of zebrafish (17,205), and both treatment with the ERS inhibitor 4-phenylbutyric acid and CHOP knockdown significantly attenuated these inhibitory effects, probably by means of either affecting β-catenin expression or inhibiting T cell factor (228).

DNA damage. Heavy metals and PAHs derived from $PM_{2.5}$ can either individually or synergistically disrupt the double-helix structure of DNA, leading to DNA damage. Valavanidis *et al* (229) identified a positive correlation between DNA reactivity and the concentration of total PAHs and transition metals. The expression and methylation of 8-oxoguanine glycosylase (OGG1) were found to be associated with the ability of PAHs to induce oxidative DNA damage (230). Epigenetic changes fulfill an important role in the regulation of PAH-induced DNA damage. H3K79 di-methylation (H3K79me2) is essential for DNA damage repair, and Zhang *et al* (231) found that exposure to PAHs reduced its overall level, revealing that it was probably serving as a marker for cellular homeostasis disruption. H3K79me2-deficient cells are more susceptible to benzopyrene-induced DNA damage than are normal cells. Improper methylation of H3K79me2 can lead to low efficiency in DNA damage repair. Therefore, after long-term exposure to PAHs, abnormal H3K79me2 may lead to genomic instability and accumulation of DNA mutations, thereby causing DNA damage. Zhao *et al* (232) found that $PM_{2.5}$ and PAHs cause significant activation of the DNA damage-susceptibility gene GADD153, resulting in a reduction of the expression of the DNA-repair genes, human MutT homolog 1 (MTH1) and X-ray repair cross complementing 1, and this inhibitory effect exceeds the clearance effect of OGG1 on damaged DNA, thereby increasing the risk of cardiac DNA damage.

OS, ionizing radiation and chemical reagents are all capable of causing DNA damage (233). Components of water-soluble $PM_{2.5}$ extracts are more likely to induce DNA oxidative damage compared with organic compounds (234). OS-induced DNA damage has been revealed to be a key mechanism of action in urban $PM_{2.5}$ pollution (235). Excessive ROS generated by pollutants induces OS, thereby mediating DNA damage in the mouse heart (236). The organic components and transition metals (including Fe, Cu, Ni and Zn) in $PM_{2.5}$ can directly generate ROS (237), which either directly causes DNA deamination and base oxidation, or indirectly induces base alkylation through lipid peroxidation (238). Therefore, $PM_{2.5}$-induced OS can lead to DNA damage. DNA damage is usually associated with cell apoptosis (239). Both ROS- or RNS-mediated DNA damage and redox-mediated inhibition of DNA-damage response proteins may lead to changes in DNA structure, thereby activating DNA-repair signaling. The latter can regulate the activities of certain apoptosis factors, further demonstrating the close association between DNA damage and cell apoptosis (240). In human or animal cells, heavy metals derived from $PM_{2.5}$ can cause various types of DNA damage, including chain breakage, diminishing the activity of endonuclease III, and damaging guanine glycosidase-sensitive sites (49). Interestingly, antioxidants and ROS scavengers can significantly block the DNA damage resulting from $PM_{2.5}$ exposure.

DNA damage can also cause cell-cycle arrest and induce apoptosis, and this may extensively disrupt the potential of progenitor cells, thereby impairing cardiac development (241). There is a large body of evidence suggesting that environmental pollutants, including $PM_{2.5}$, may attack DNA by means of OS (45). Excessive ROS production during zebrafish embryonic development has been revealed to lead to DNA damage and apoptosis (196). Elevated levels of 8-OHdG and γ-h2ax were observed in the zebrafish embryonic heart, although these were significantly circumvented by treatment with the

ROS scavenge, NAC. However, NAC could not completely reverse the DNA-damage signaling processes induced by $PM_{2.5}$, suggesting that OS is only partly responsible for causing the DNA damage (242). The cardiac DNA damage caused by $PM_{2.5}$ is most likely to be involved in multiple signaling pathways and synergistic effects of multiple molecules, and further in-depth exploration in this regard is required.

Ca^{2+} homeostasis disorder. Ca^{2+} is essential for cardiac automation, electrical conduction, excitation transcription coupling and maintenance of vascular tone. It is not only necessary for cardiovascular contraction and relaxation, but it also serves a crucial role as a second messenger in signal-transduction pathways (243). A Ca^{2+} imbalance can lead to various types of cardiomyopathy, and Ca^{2+} homeostasis is often considered a key factor in heart disease. Therefore, accurate Ca^{2+} signaling is crucial for maintaining cardiac function. Exposure to $PM_{2.5}$ preferentially affects the expression of Ca^{2+} signaling-associated genes in human pluripotent stem cell-derived cardiomyocytes, thereby increasing the likelihood of arrhythmia (244). $PM_{2.5}$-mediated OS and Ca^{2+} influx in endothelial cells cause cellular damage, ultimately leading to cell death (245). $PM_{2.5}$ exposure may also increase the concentration of intracellular free Ca^{2+} ions by altering the expression of Ca^{2+} channel-associated proteins in the mouse heart (246). Ca^{2+} also stimulates the assembly of contractile cytoskeleton structures in developing cells. The endoplasmic reticulum is known to have Ca^{2+} channels which play a crucial role in Ca^{2+} regulation (247). An increase in OS will lead to oxidative inactivation of endoplasmic reticulum Ca^{2+}-ATPase, thereby increasing cytoplasmic Ca^{2+} levels (248). Numerous details of the mechanism underlying $PM_{2.5}$-mediated intracellular Ca^{2+} imbalance in OS have been elucidated (246).

Cd can induce lipid abnormalities through ERS and Ca^{2+} imbalance (249). In addition, Cd disrupts Ca^{2+} homeostasis, affects vital genes associated with Ca^{2+} channels, and leads to excessive Ca^{2+} in the cytoplasm. Following exposure to Cd, the IrxA cluster, Mefs and Tbxs family transcription factors were found to be downregulated, suggesting the impairment of cardiac transcription, abnormal expression of cardiac markers (TnnT2, TnnC1, Gata4, Gata6 and Nkx2-5), and the inhibition of cardiomyocyte maturation and differentiation (163).

4. Conclusion

Given the enormous environmental harm caused by $PM_{2.5}$, society in its entirety can take certain actions to combat the damaging effects, including governmental policies, urban planning, technology and raising social ecological awareness. The strategies for regulating $PM_{2.5}$ include reducing dust emissions during construction, transportation and other processes (including through dust removal and filtration), controlling vehicle and industrial emissions (through promoting hybrid or electric vehicles), and transitioning from traditional energy sources to renewable energy sources (such as hydro, solar, geothermal, wind and nuclear energy). One of the most important aspects is to reduce fossil fuel-associated $PM_{2.5}$, as fossil fuel combustion occupies a central role in the health impacts associated with $PM_{2.5}$. $PM_{2.5}$ air pollution derived from fossil fuel combustion has been linked to over 10 million premature deaths (250). These ubiquitous emissions from fossil fuel combustion are one of the biggest contributors to the adverse effects of $PM_{2.5}$ on health. The particles from fossil fuel combustion contain abundant transition metals [such as Ni, vanadium (V), Fe and Cu] that readily participate in redox reactions that generate OS. At the same time, sulfur (S), which is $PM_{2.5}$-adsorbent, increases the bioavailability of the transition metals, greatly enhancing the possibility of fossil fuel-associated $PM_{2.5}$ being a causative agent of OS and endangering overall health (251). In 2019, environmental air pollution caused ~7 million deaths worldwide (252). With the intensification of climate change, environmental air pollution is worsening. Since 1990, the number of deaths caused by environmental air pollution has increased by 51%, and continues to rise (253). Climate change poses a serious threat to human health, with the primary driving factor determined to be the sharp increase in greenhouse gas emissions that are caused by extensive fossil fuel combustion. A total of ~85% of air particulate pollution is caused by fuel combustion, and almost all air pollution is associated with sulfur oxides and nitrogen oxides (254). Therefore, reducing the use of fossil fuels, and the dependence on fossil fuels, is of great significance for optimizing the health benefits of mitigating climate change.

With the intensification of global air pollution, exposure to $PM_{2.5}$ has been found to correlate closely with the incidence of CHD. The reported molecular mechanisms underlying the $PM_{2.5}$-exposure-induced cardiac developmental toxicity mainly include: interference with genes related to cardiac development, dysfunction of genes associated with heart function, OS, inflammation, mitochondrial impairment, epigenetic modification, ERS, autophagy, apoptosis, AhR signaling, Wnt signaling, DNA damage and disorders of Ca^{2+} homeostasis (Fig. 1). Due to the complexity, diversity and unclear toxicity attributed to $PM_{2.5}$, continuing investigations on cardiac development toxicity derived from $PM_{2.5}$ exposure inevitably face challenges, and it is necessary to further elucidate the mechanisms underlying $PM_{2.5}$-induced CHD in our future studies.

As a key factor in cardiac development and homeostasis, AhR signaling fulfills a key role in cardiac development. The interruption of AhR function during development can lead to potential cardiac developmental toxicity, and this comprises a number of dysregulated signaling pathways that participate in cardiac development, function and metabolism. At the same time, AhR is also a target for environmental factors that may disrupt the homeostasis of AhR, laying the foundation for CHD. Due to the widespread presence of AhR antagonists and methyl donors such as flavonoids, curcumin and betaine, that are found in daily foods, these may serve as favorable candidates for addressing the abnormal activation of AhR and changes in m6A RNA methylation derived from $PM_{2.5}$ exposure. Moreover, phytochemicals are able to alleviate the adverse effects of $PM_{2.5}$ exposure on human health, predominantly via inhibiting OS, ERS and Fe deposition, which subsequently alleviates inflammatory reactions, along with regulating autophagy. Taken together, these findings provide a potential approach for therapeutic intervention with regard to the cardiac developmental toxicity caused by $PM_{2.5}$ exposure.

Although mitochondria are the most important source of ROS, increasing evidence has suggested that other organelles as the potential sources of ROS, such as the endoplasmic

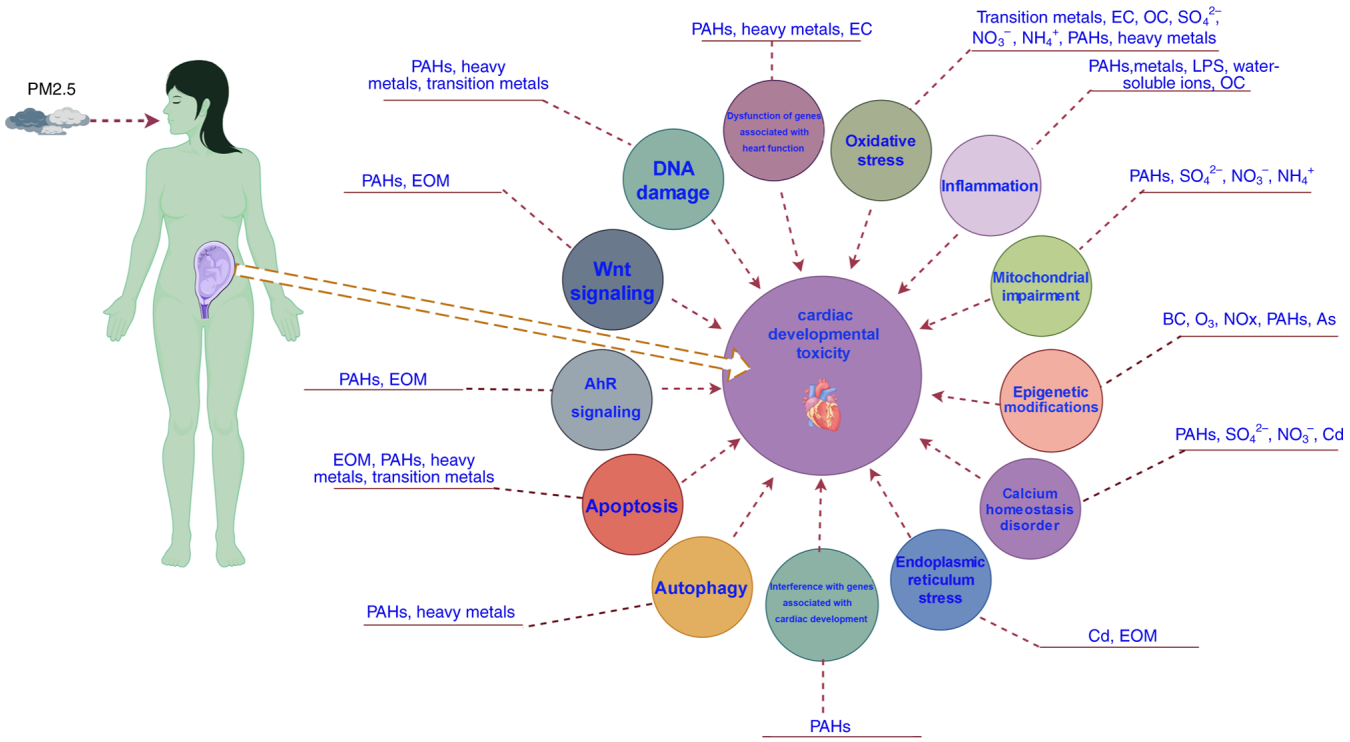

Figure 1. The underlying mechanisms involved in $PM_{2.5}$-induced cardiac developmental toxicity (drawn using Figdraw.com). PAHs, EOM, EC/BC, inorganic ions, metals and OC are different sources of $PM_{2.5}$. After being inhaled in the lung, $PM_{2.5}$ can enter the fetus through the air-blood barrier and placental barrier, as well as induce adverse reactions such as inflammation and OS in the mother and placenta to generate large amounts of harmful products such as pro-inflammatory cytokines and reactive oxygen species, thereby causing cardiac developmental toxicity to the fetus. The underlying mechanisms involved include: interference with genes related to cardiac development, dysfunction of genes associated with heart function, OS, inflammation, mitochondrial impairment, epigenetic modification, endoplasmic reticulum stress, autophagy, apoptosis, Aryl hydrogen receptor signaling, Wnt signaling, DNA damage and disorders of Ca^{2+} homeostasis. PAHs: mainly derived from natural fires and volcanic eruptions, transportation, industrial production, and incomplete combustion; Heavy metals: mainly from daily power generation, industrial production and automobile exhaust emissions; EC/BC: mainly from direct combustion emissions, including industrial pollution, agricultural pollution, transportation pollution and domestic pollution sources; Transition metals: mainly from fossil fuel combustion, industrial processes, road dust and construction; EOM: mainly derived from direct emissions and secondary reactions related to combustion; Inorganic ions (including SO_4^-, NO_3^- and NH_4^+): mainly derived from secondary reactions. OC: mainly from motor vehicle emissions, coal-fired emissions, biomass combustion, catering fumes and secondary reactions. PAHs, polycyclic aromatic hydrocarbons; EOM, extractable organic matter; EC, element carbon; OS, oxidative stress; BC, black carbon; OC, organic carbon.

reticulum, peroxisomes and cell membranes, are also important. Therefore, understanding the sources of ROS is of great significance for targeted therapy, dosage selection and pollution control. Considering the high energy consumption of the heart and the role of mitochondria as the body's energy production factory, mitochondria may be a promising therapeutic target for the prevention and treatment of CHD. Given the deepening understanding of mitochondrial biology, the widespread application of large-scale experimental animal models, and the rapid development of new scientific and technological advancements, mitochondrial medicine may become a realistic therapeutic option in the near future.

The molecular mechanisms underlying the toxicity of $PM_{2.5}$ exposure to cardiac development are markedly more complex than were previously considered, and there are numerous remaining issues to be addressed; for example, how interactions between various cells (such as crosstalk among endothelial, smooth muscle and immune cells) may have a role in this process, and what key factors and signaling pathways are involved in the cardiac developmental toxicity that is induced by $PM_{2.5}$ exposure. It remains unclear how these signaling pathways interact with each other, and how the concentration and duration of $PM_{2.5}$ exposure affect them. These issues retain their significance, and merit further in-depth research. In addition, the chemical composition of $PM_{2.5}$ is complex, with different sources and toxic effects, and the components of $PM_{2.5}$ vary differentially across different regions and seasons. Therefore, it is difficult to form systematic research conclusions. In addition, further investigations are needed to determine whether the toxic effects of $PM_{2.5}$ on cardiac development are mediated solely with $PM_{2.5}$ functioning as a carrier, or whether $PM_{2.5}$ interacts with the toxic substances it carries. Therefore, the interactions among different components of $PM_{2.5}$ and their combined effects with other air pollutants should be also explored. Evidently, it is necessary to perform additional studies on the spatiotemporal distribution characteristics and physicochemical properties of $PM_{2.5}$, and analyze its effects on cardiac development at different stages, locations and levels, including an assessment of the various physicochemical components.

In summary, the present review elaborates the potential molecular mechanisms underlying the cardiac developmental toxicity induced by gestational $PM_{2.5}$ (including some of its specific components) exposure, and the complexity presents numerous challenges and opportunities for future investigations. Understanding the interplay of various signaling

pathways during this process, alongside the concentration and duration of $PM_{2.5}$ exposure, will be crucial for advancing our knowledge in this field. In addition, exploring the individual and synergistical cardiac developmental toxicity effects induced by differential $PM_{2.5}$ components will be vital for developing effective intervention measures and regulatory strategies. In order to deepen our understanding of the cardiac developmental toxicity induced by $PM_{2.5}$, future researches should focus on longitudinal studies evaluating the long-term effects of early exposure on the cardiac outcomes. This will provide insights into potential interventions to mitigate these effects. Addressing these multifaceted challenges will provide supports for public health policies to reduce exposure to $PM_{2.5}$ and improve population health outcomes. Ultimately, a comprehensive understanding of $PM_{2.5}$'s toxicological effects will contribute to the scientific community and empower policymakers to implement effective strategies safeguarding public health, particularly among vulnerable populations.

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Availability of data and materials

The data generated in the present study are included in the figures and/or tables of this article.

Authors' contributions

XM, WD and ZS conceived and designed the study. XM and WD collected the literature. XM, WD and ZS analyzed the literature, and drafted and reviewed the manuscript. Data authentication is not applicable. All authors read and approved the final version of the manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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