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Review article

Air pollution, environmental chemicals, and smoking may trigger vitamin D deficiency: Evidence and potential mechanisms

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ABSTRACT

Beyond vitamin D (VD) effect on bone homeostasis, numerous physiological functions in human health have been described for this versatile prohormone. In 2016, 95% of the world's population lived in areas where annual mean ambient particulate matter (< 2.5 μm) levels exceeded the World Health Organization guideline value (Shaddick et al., 2018). On the other hand, industries disperse thousands of chemicals continually into the environment. Further, considerable fraction of populations are exposed to tobacco smoke. All of these may disrupt biochemical pathways and cause detrimental consequences, such as VD deficiency (VDD). In spite of the remarkable number of studies conducted on the role of some of the above mentioned exposures on VDD, the literature suffers from two main shortcomings: (1) an overview of the impacts of environmental exposures on the levels of main VD metabolites, and (2) credible engaged mechanisms in VDD because of those exposures. To summarize explanations for these unclear topics, we conducted the present review, using relevant keywords in the PubMed database, to investigate the adverse effects of exposure to air pollution, some environmental chemicals, and smoking on the VD metabolism, and incorporate relevant potential pathways disrupting VD endocrine system (VDES) leading to VDD. Air pollution may lead to the reduction of VD cutaneous production either directly by blocking ultraviolet B photons or indirectly by decreasing outdoor activity. Heavy metals may reduce VD serum levels by increasing renal tubular dysfunction, as well as downregulating the transcription of cytochrome P450 mixed-function oxidases (CYPs). Endocrine-disrupting chemicals (EDCs) may inhibit the activity and expression of CYPs, and indirectly cause VDD through weight gain and dysregulation of thyroid hormone, parathyroid hormone, and calcium homeostasis. Smoking through several pathways decreases serum 25(OH)D and 1,25(OH)2D levels, VD intake from diet, and the cutaneous production of VD through skin aging. In summary, disturbance in the cutaneous production of cholecalciferol, decreased intestinal intake of VD, the modulation of genes involved in VD homeostasis, and decreased local production of calcitriol in target tissues are the most likely mechanisms that involve in decreasing the serum VD levels.

Abbreviations: AQI, air quality index; BaP, Benzo[*a*]Pyrene; B-HCH, β-Hexachlorocyclohexane; BLL, blood lead level; BMD, bone mineral density; BMI, body mass index; BPA, bisphenol A; COPD, chronic obstructive pulmonary disease; CS, cigarette smoke; CSE, cigarette smoking extract; CYPs, cytochrome P450 mixed-function oxidases; DBP, vitamin D binding protein; DDE, Dichlorodiphenyldichloroethylene; DDT, Dichlorodiphenyltrichloroethane; DEHP, di (2-ethylhexyl) phthalate; DHC, dehydrocholesterol; DU, depleted uranium; EDCs, endocrine-disrupting chemicals; EU, enriched uranium; iPTH, intact parathyroid hormone; IQR, interquartile range; IU, international unit; MCPP, mono-3-carboxypropyl phthalate; MMPs, matrix metalloproteinases; OC, organochlorine; PCB, polychlorinated biphenyl; PM, particulate matter; PND, post-natal day; POPs, persistent organic pollutants; TH, thyroid hormone; PTH, parathyroid hormone; S-25(OH)D, serum 25(OH)D; RXR, retinoid X receptor; SEI, sun exposure index; VD, vitamin D; VDD, vitamin D deficiency; VDES, vitamin D endocrine system; VDR, vitamin D receptor

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1. Introduction

Vitamin D is provided either through exposure to sunlight, which is the main source or through intake from diet, which is supplementary (Hansdottir et al., 2008; Holick, 2006). To sustain the human health, the presence of a sufficient level of VD is compulsory. Insufficiency and deficiency of VD have been reported in different climates and geographical regions. It is estimated that one billion individuals in the world suffer from VD deficiency (VDD) in all age groups (Holick, 2007; Holick and Chen, 2008). Accordingly, VDD has been identified as one of the important public health concerns globally, and particularly in the Middle East region (Palacios and Gonzalez, 2014). Due to the underlying role of this member of the steroid hormone family in biochemical processes, VD has received a growing attention during the last decades. Along with the understanding of VD metabolism, its related disorders and therapeutic capabilities have been listed as one of the foremost priorities for public health.

Although there is no precise estimation of the global burden of VD deficiency, an array of investigations conducted by Lips and Van Schoor provided a global overview of VD status. Based on studies performed on the national status of VD around the globe, it turned out that VD deficiency and insufficiency is very common in most countries, mainly in the Middle East, India, China, and Mongolia. Lips and Van Schoor also found that at risk groups for VDD include young children with low birth weight, pregnant women, non-western immigrants and older individuals (Lips, 2010; Lips and van Schoor, 2011; Van Schoor and Lips, 2017). Studies have reported that VDD (< 30 nmol/l) prevalence in infants has been 86% in Iran, 61% in India, and 51% in Turkey (Roth et al., 2018). As VDD is considered as a contributing factor to human diseases, studying the interactions between VD metabolism and environmental agents seems to be noteworthy, especially to understand links between environmental exposures and the pathogenesis of chronic disorders. Although adequate exposure to inducible radiation of the sun and adequate intake by dietary sources are key factors in maintaining an acceptable level of VD, there is persuasive evidence demonstrating that there are other environmental factors that interfere in VD endocrine systems (VDES). Therefore, studying the impacts of environmental pollutants on VD metabolism seems necessary.

In 2016, 95% of the world's population lived in areas where ambient particulate matter < 2.5 μm ($PM_{2.5}$) levels exceeded the World Health Organization guideline value of 10 μg/m^3 (Shaddick et al., 2018). On the other hand, industries disperse thousands of chemicals into environment. Further, considerable fraction of populations are exposed to tobacco smoke. All of these may disrupt biochemical pathways and cause detrimental consequences like VD deficiency (VDD). In addition, we are in need of mechanistic studies to declare how exposure to these exposures disrupt biochemical events and participate in the pathogenesis of disorders through decreasing the levels of active metabolites of VD. In this study, we aimed to provide a mechanistic overview of the aftermaths of exposure to air pollution, some environmental chemicals and tobacco smoke related to dysfunctional VDES accompanied with the declined serum levels of two main metabolites of VD including 25-hydroxyvitamin D (25(OH)D, Calcifediol) and 1α,25-dihydroxyvitamin D (1,25$(OH)_2$D, Calcitriol).

2. Material and methods

Exposure to air pollution, some environmental chemicals, and smoking, which are implicated directly or indirectly in disrupting VDES and decreasing the serum levels of two main metabolites of VD were investigated in this review. Briefly, the PubMed Database search was performed on May 3nd 2018 using a combination of the following keywords: (“Air Pollution”, “Heavy Metals”, “Endocrine Disruptors”, “Halogenated Hydrocarbons”, “Bisphenol A” (BPA), “Phthalate”,

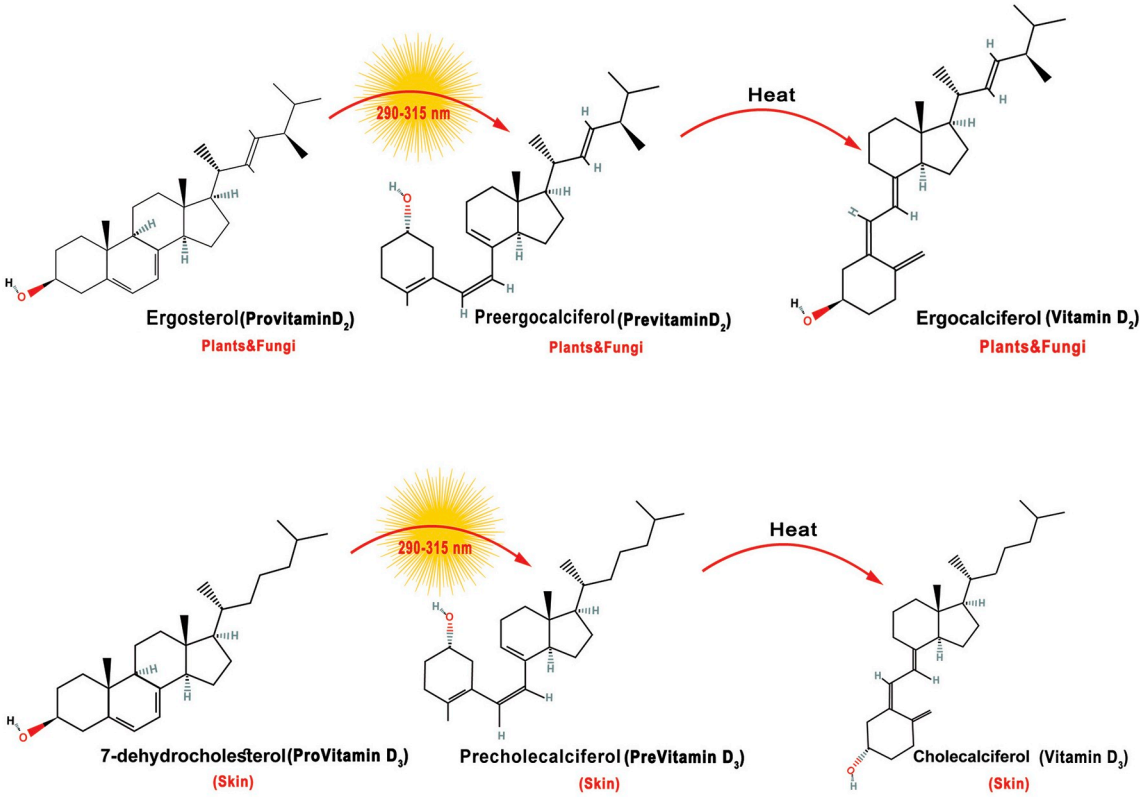

Fig. 1. The photosynthesis of ergocalciferol (D_2) and cholecalciferol (D_3). The upper process shows the synthesis of vitamin D_2 from ergosterol with the help of UVB radiation in plants and fungi. The lower process displays the photosynthesis of vitamin D_3 from 7-dehydrocholesterol (7-DHC) in keratinocytes—the skin cells responsible for the cutaneous production of vitamin D_3.

"Smoking", "Tobacco Use") AND ("Vitamin D"). Moreover, the reference lists from included and relevant review articles were manually searched. In order to include all available studies till the day, we used Google Scholar as an additional source to fill in any probable gap. Search strategy is presented in online Supplementary File 1.

There are numerous studies that have proposed the exposure to tobacco smoke as one of lifestyle risk factors for VDD; however, we only included those which had specifically focused on the relationship between smoking and the VD levels. Finally, 74 studies were included in the review. Tables 1 and 2 provide a summary of the included articles in this review.

3. Results and discussion

3.1. Synthesis of VD

As a member of the fat-soluble group of secosteroids (steroid molecules with a broken ring), VD plays a pivotal role in the metabolism of calcium and phosphate, as well as, other biological processes. As it is shown in the Fig. 1, there are two main types of VD including D_2 (ergocalciferol) and D_3 (cholecalciferol). Both of them could be provided through exogenous sources. The former is originated from the ultraviolet B (UVB) irradiation of the ergosterol in plants and fungi, and the latter is found in the dietary sources, particularly in oily fish, and is produced in the skin as well (the main and endogenous source) (Holick, 2006). Vitamin D_3 can be synthesized in the skin without any enzymatic reaction. It is produced from 7-dehydrocholesterol (7-DHC) via a two-step process in which UV light (wavelengths of 290–315 nm) radiation from the sun photolyzes 7-DHC (provitamin D_3) to precholecalciferol (previtamin D_3) in the plasma membrane of human skin keratinocytes. Afterward, in a heat-dependent process, previtamin D_3 instantly converts to vitamin D_3 (Holick, 2007). Skin pigmentation and UVB intensity are two significant factors in the rate of vitamin D_3 formation (Holick et al., 1980; MacLaughlin et al., 1982). Thus, all factors which may limit sun exposure (whether periodically or locally) can affect the production of the VD.

D_2, as the first VD analog, is structurally different from D_3, resulting in its lower affinity to VD-binding protein (DBP), which in turn leads to its faster clearance from the circulation, limited conversion to the active form, and altering catabolism by the enzyme 24-hydroxylase (CYP24A1) (Hollis, 1984; Houghton and Vieth, 2006). As a result, D_2 supplementation does not result in high serum levels of VD as much as D_3 (Viljakainen et al., 2006).

3.2. VD metabolism

There are three main steps in the VD metabolism consisting of 25-hydroxylation, 1α-hydroxylation, and 24-hydroxylation performed by cytochrome P450 mixed-function oxidases (CYPs), enzymes located in endoplasmic reticulum (ER) (e.g., CYP2R1) or in the mitochondria (e.g., CYP27A1, CYP27B1, and CYP24A1) (Bikle, 2014). The mentioned types of VD (D_2 and D_3) are physiologically inactive and therefore in need of two sequential hydroxylations to turn into the biologically active form (Fig. 2). After transportation of VD by DBP to the liver (the major source of 25(OH)D production), it is hydroxylated by a number of CYPs with 25 hydroxylase activity resulting in the formation of 25(OH)D (Christakos et al., 2010). Since a homozygous mutation of the CYP2R1 gene has been observed in the patients with low circulating levels of 25(OH)D and classic symptoms of VDD, it could be suggested that CYP2R1 is the key enzyme required for 25-hydroxylation of VD (Cheng et al., 2004).

In the second step, 25(OH)D, as the major circulating form of VD and the standard indicator of VD status, is transported to the kidney for the next hydroxylation. 1α-hydroxylase (CYP27B1) is the most abundant enzyme which has the capability to hydroxylate the position of carbon 1 of the A ring leading to the generation of the hormonally active form of VD, $1,25(OH)_2D$. It should be pointed out that the kidney is the major, if not the sole, source of circulating levels of $1,25(OH)_2D$ (Bikle, 2014). As it can be seen in the Fig. 2, low levels of calcium and phosphate, as well as the elevated level of parathyroid hormone (PTH) resulted from hypocalcemia stimulate the production of $1,25(OH)_2D$ (Murayama et al., 1999). As a result, increased levels of VD and calcium cause diminishing expression of PTH and VD receptor (VDR). VDR as the principal mediator is responsible for cellular effects of VD through natural ligand with $1,25(OH)_2D$. Concisely, it can be said that $1,25(OH)_2D$ levels are downregulated via its own production and the level of serum calcium, while PTH induces its renal production (Bikle, 2014; Christakos et al., 2010).

The last but not least step in the metabolism of VD is that it is responsible for the hydroxylation of VD through the CYP24A1 which has 24-hydroxylase activity and results in the water-soluble biologically inactive calcitroic acid. Although the enzyme introduce hydroxyl into both 25(OH)D and $1,25(OH)_2D$, the preferred substrate for 24(OH)ase is $1,25(OH)_2D$ (Omdahl et al., 2002; Shinki et al., 1992). Accordingly, the control of $1,25(OH)_2D$ level within tissues can be taken into account as the foremost function of 24(OH)ase. This process can occur through the catabolism of $1,25(OH)_2D$ to $1,24,25(OH)_3D$ or by decreasing the reservoir of 25(OH)D via its catabolism to $24,25(OH)_2D$ (Christakos et al., 2010). This process may prevent VD intoxication which could come from more than normal levels of 25(OH) and $1,25(OH)_2D$ (Bikle, 2014).

3.3. Functions and disorders related to VD

Thanks to the extensive studies on the VD metabolism during the last decades, there is growing evidence asserting the significant role of VD inadequacy in the pathogenesis of a wide array of chronic diseases. Even though there is no unanimity on the optimal level of serum 25-hydroxyvitamin D (S-25(OH)D), there is an implicit agreement regarding the definition of VDD. Previous studies reported that S-25(OH)D < 20 ng/ml is considered as VD deficiency, 20 to 30 ng/ml is insufficiency, 30 to 60 ng/ml is a sufficient level, and > 150 ng/ml is intoxication (Holick, 2007, 2009).

Disturbance in the metabolism of the active form of VD ($1,25(OH)_2D$) is considered as a cause of VDD (Clements et al., 1992; Holick, 2007). The conversion of the storage form of VD to its active form stimulates the absorption of intestinal calcium and phosphate, which in turn contribute to the bone health. This function of VD in the homeostasis of calcium and phosphate plays an essential role in musculoskeletal health as its deficiency could lead to osteoporosis, osteomalacia, decreased bone mineral density, and increased risk of fragility fractures (Christodoulou et al., 2013). Potentially, the circulating levels of $1,25(OH)_2D$ affect functions of all tissues and cells possessing VDR, particularly active T and B lymphocytes, breast, colon, prostate, and heart skeletal muscle (Holick, 2006; Mathieu and Adorini, 2002; Nagpal et al., 2005). Moreover, it has been observed that aside from kidney, a broad range of tissues, mainly brain (neurons and glial cells), lung (lung epithelial cells), colon (epithelial cells and parasympathetic ganglia), prostate (normal (NP96-5), benign prostatic hyperplasia (BPH) cells), skin (keratinocyte), and breast (normal lobules and ducts tissue), as well as macrophages, have the capability to locally express 25-hydroxyvitamin D-1α-hydroxylase, and produce $1,25(OH)_2D$. Therefore, they regulate the expression of genes involving in their functions, especially cell proliferation and differentiation (Bikle, 2011; Eyles et al., 2005; Hansdottir et al., 2008; Schwartz et al., 1998; Townsend et al., 2005; Zehnder et al., 2001). Thus, in addition to musculoskeletal consequences of VD inadequacy, increasing experimental and epidemiological evidence depicted that VDD can be involved in the pathogenesis and/or progression of chronic illnesses, such as many common cancers (colon, breast, and prostate) autoimmune diseases (multiple sclerosis and type 1 diabetes mellitus, inflammatory bowel disease, systemic lupus erythematosus), hypertension, cardiovascular diseases, and

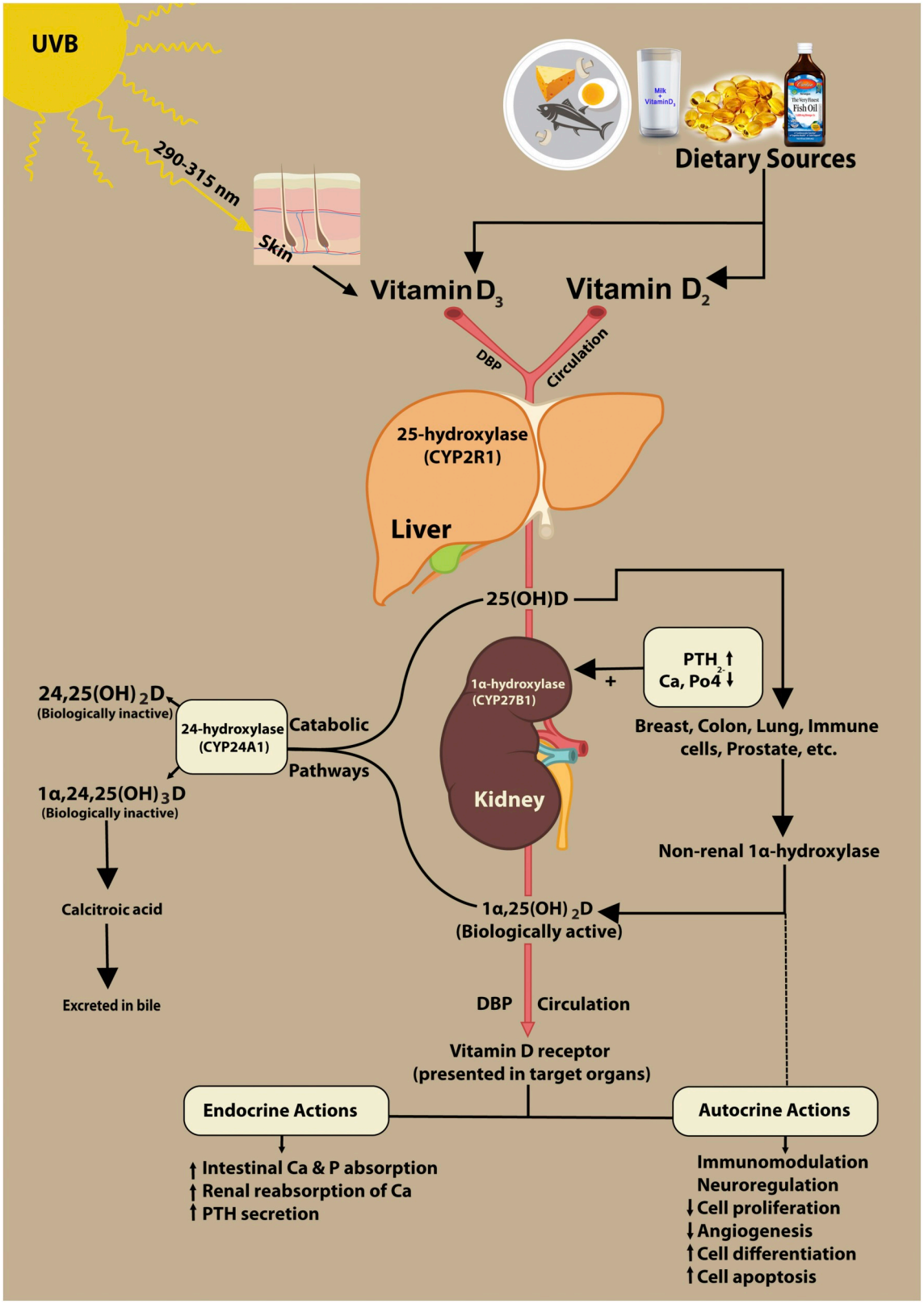

Fig. 2. VD endocrine system (VDES). VD is mainly synthesized in the skin cells and can be found in dietary sources as well. Through a two-stage hydroxylation process, VD firstly converts to 25(OH)D and then is activated to $1,25(OH)_2D$. Liver and kidney are two principal organs where 25(OH)D and $1,25(OH)_2D$ are produced, respectively. With the help of DBP and circulating system, $1,25(OH)_2D$ is transferred into the target organs possessing VD receptor (VDR) and results in autocrine and endocrine actions.

neurological disorders (Plum and DeLuca, 2010; Wang et al., 2017).

Based on the mentioned broad role of VD in human health and adverse health effects derived from its deficiency, numerous efforts have been made to evaluate its analogs in attenuation and treatment of all aforementioned disorders. Antiproliferation, prodifferentiation, immunomodulation, antiangiogenesis, and apoptosis are among the most protective functions that can be exerted by VD supplementations and analogs (Adorini and Penna, 2008; Holick, 2006). Such noncalcemic mechanisms are recruited by VD analogs, especially $1,25(OH)_2D$ to treat various types of disorders (Bikle, 2014). It has been shown that VD analogs can be taken into account as preventative and therapeutic agents by which the progression and risk of cancers (Deeb et al., 2007), autoimmune diseases (Adorini and Penna, 2008), heart disorders, and musculoskeletal illnesses would be reduced to a great extent (Plum and DeLuca, 2010; Souberbielle et al., 2010).

3.4. Environmental contaminants

Owing to a plethora of studies performed on the detrimental health effects of anthropogenic pollutants, solid evidence has been provided during the last years associating VDD with exposure to environmental contaminants including endocrine-disrupting chemicals (EDCs). Interestingly, both EDCs exposure and VDD are heavily implicated in adverse developmental, neurological, cardiovascular, metabolic and immune effects in humans (Schug et al., 2011; Wang et al., 2017).

During the last decades, there has been an overwhelming urge among researchers to investigate the possible health impacts posed by EDCs and potential EDCs, which are anthropogenic toxic materials in our environment, food, and consumer products. Pesticides, metals, bisphenol A (BPA), phthalates, polycyclic aromatic hydrocarbons (PAHs), and polyhalogenated compounds are on the top of the most damaging EDCs, which damage human health (Frye et al., 2012). According to the definition of U.S. Environmental Protection Agency (EPA), an endocrine-disrupting chemical is “an exogenous agent that interferes with synthesis, secretion, transport, metabolism, binding action, or elimination of natural blood-borne hormones that are present in the body and are responsible for homeostasis, reproduction, and developmental process” (Diamanti-Kandarakis et al., 2009). On the other hand, VD should be considered as a prohormone that can be developed to its hormonal form ($1,25(OH)_2D$) through the VD endocrine system (VDES) depicted in Fig. 2. All tissues possessing the enzyme 1α-hydroxylase, especially the kidney, could be taken into consideration as endocrine glands which convert 25(OH)D to the hormonal form of $1,25(OH)_2D$. It is noteworthy that investigators have shown > 36 target organs with VDR as a receptor for steroid hormone $1,25(OH)_2D$ (Bouillon et al., 1995; Norman, 2008).

EDCs have been shown to affect the biosynthesis pathways of steroid hormone and thyroid hormone (TH) levels (Boas et al., 2012; Sanderson, 2006). Since VD is similar to steroid hormones in terms of molecular structure and biological functions and its nuclear receptor belong to the same superfamily of proteins as steroid and thyroid hormone receptors (Norman, 2008), it is highly likely that EDCs affect VDES. Consequently, it seems plausible to state that all endocrine systems in general and VDES in particular, can be disrupted by environmental chemical exposures. Such a deductive argument originates from this fact that EDCs activate the same receptors and signaling pathways as hormones and act at low concentrations. They are subjects to the same biological regulatory systems as hormones (Schug et al., 2011).

As indoor and outdoor air pollutants, tobacco smoke, heavy metals and persistent organic pollutants (POPs) can behave like EDCs, we intend to incorporate all human and experimental studies that reported rising prevalence of VDD and disruption of the VDES because of exposure to these mentioned risk factors. To bring convincing associations, interactions between the chemicals and VDES will be mechanistically explained as far as studies provide enough evidence.

3.4.1. Air pollutants

As mentioned above, sun exposure plays an underlying part in VDES. Therefore, every factor that has the potency to restrict the absorption of sunlight by the skin would be capable of dysfunction in VD metabolism fundamentally. Epidemiological and clinical studies represent an association between atmospheric pollution and hypovitaminosis D (Agarwal et al., 2002; Baïz et al., 2012; Calderón-Garcidueñas et al., 2015; Calderón-Garcidueñas et al., 2013; Hosseinpanah et al., 2010; Kelishadi et al., 2014; Manicourt and Devogelaer, 2008). In megacities with a high level of air pollutants, especially ozone, particulate matter (PM), and sulfur dioxide, the UVB photons would be effectively absorbed by these pollutants, diminishing the cutaneous photosynthesis of previtamin D_3 (Gorham et al., 1989; Holick, 1995; Hoseinzadeh et al., 2018). This could contribute to the modulation of immune responses subsequent to a substantial decrease in the level of VD (Mousavi et al., 2017). In an interesting cross-sectional study, Manicourt and colleagues evaluated interactions between exposure to tropospheric ozone and sunlight affecting the percentage of subjects with VD inadequacy in two groups of postmenopausal women from Brussels or the countryside engaged in outdoor activities. Participants did not differ in mean ages, body mass indices, and VD intakes; nevertheless, urban residents were exposed to ozone levels 3-fold higher than rural inhabitants. Notwithstanding that the urban inhabitants benefited from higher mean sun exposure index (SEI) than rural ones (113 vs. 87; $P < 0.001$), they had a higher prevalence of 25(OH)D < 30 ng/ml (84% vs. 38%). It should be pointed out that after adjusting for SEI, 25(OH)D was two times higher in rural residents, and after adjusting for 25(OH)D, SEI was three times higher in urban residents (Manicourt and Devogelaer, 2008). In comparison to the countryside, residents in the urban areas with a high level of air pollution may be discouraged from engaging outdoor activities leading to high prevalence of VDD (Bailey et al., 2012). Overall, results of Manicourt et al. should be interpreted with caution as the ozone concentrations are typically higher in rural areas compared to urban areas as nitrogen oxides originated from exhaust emissions scavenge the ozone and reduce it in the urban areas (McConnell et al., 2006). However, some other local conditions in Brussels might be responsible for the reported 3-fold higher ozone concentrations compared with rural areas.

In a recent study performed in Mexico, it was reported that exposure to high concentration of $PM_{2.5}$ could lead to S-25(OH)D < 30 ng/ml in 87% of Mexico City metropolitan area normal weight children compared to controls (Calderón-Garcidueñas et al., 2015). In Mexico City, an environment characterized by ozone and PM levels above standard values and decreased UV light, children had an insufficient VD intake and spent less time outdoors than controls ($P < 0.001$) (Calderón-Garcidueñas et al., 2013). Since it has been shown that air pollution is capable of reducing UV light by 20% on average (Acosta and Evans, 2000) in Mexico City, it could be inferred that in the setting of high concentration of air pollutants, children have gotten less UV light exposure. Furthermore, spending less time outdoor synergistically reduce VD availability. As a matter of fact, an atmospheric situation with a high level of pollutants and dust causes high haze in which the visibility considerably reduces because of the decreased penetration of sunlight. It is proposed that sunlight-blocking haze lessens the exposure to sun's VD inducing radiations. Agarwal et al. compared the VD level of two comparable groups of 9 to 24-month-old toddlers lived in two different areas of India in terms of the level of atmospheric pollution. The mean serum concentration 25(OH)D of children from Mori Gate, well-known for a high level of air pollution, was 12.4 ng/ml, compared with 27.1 ng/ml in those who lived in Gurgaon area with less polluted air ($P < 0.001$). Moreover, the mean haze score in the Mori Gate area (2.1) was significantly lower ($P < 0.05$) than in the Gurgaon area (2.7), indicating less solar UVB reaching the ground in Mori Gate (Agarwal et al., 2002).

Through the study of a cohort group in Paris, the relationship between gestational exposure to two urban air pollutants (PM_{10} and NO_2) and 25(OH)D cord blood serum level was inquired in 375 mother-child pairs. Baïz and colleagues found that maternal exposure to the urban

pollutants, in particular during late pregnancy, may contribute to lower VD levels in offspring. After adjustment, log-transformed 25(OH)D declined by 0.15 units (P = 0.05) and 0.41 units (P = 0.04) for an increase of 10 ng/m^3 in NO_2 and PM_{10} pregnancy levels, respectively (Baïz et al., 2012). Studies performed in Tehran and Isfahan, two high air-polluted metropolises in Iran, also revealed that there is a negative association between air quality and VD status (Hosseinpanah et al., 2010; Kelishadi et al., 2014). Kelishadi and colleagues conducted a cross-sectional study of 100 children aged 4–10 years from various areas of Isfahan city with different levels of air pollution in order to investigate the association between air quality index (AQI) and serum concentration of 25(OH)D. After adjustment for age, gender, body mass index (BMI), diet and pattern of physical activity, by a multiple linear regression, they demonstrated an inverse association between AQI and 25(OH)D, which properly justified the high prevalence of VDD among Isfahanian children. According to the data related to the dietary habits obtained through validated questionnaires, they reported that dietary intake of VD was not sufficiently low to explain the very low level of S-25(OH)D (Kelishadi et al., 2014). In a similar study, Hosseinpanah et al. compared two groups of healthy women from Tehran (higher-polluted city) and Qazvin (lower-polluted city) concerning VD status. The mean ± SD of S-25(OH)D level was markedly higher in Qazvinian women (18 ± 11) compared with Tehranians (13 ± 7) (P-value < 0.001). The prevalence of severe VDD (25(OH)D < 10 ng/ml) and 25(OH)D of 10–20 ng/ml among women in the high-polluted city were 36% and 54%, respectively, while they were estimated 31% and 32% in women from Qazvin (Hosseinpanah et al., 2010).

3.4.2. Heavy metals

Due to the ubiquity of toxic metals in the environment and their role as putative endocrine disruptors, it is necessary to study those metals that can negatively affect steroid hormones, particularly VD. In this regard, various studies have been demonstrated that heavy metals, especially cadmium (Cd) and lead (Pb), as well as radioactive metals, in particular, uranium (U) and ^{137}cesium (^{137}Cs) are capable of interfering hormonal systems including VDES (Dyer, 2007).

3.4.2.1. Cadmium and lead. Since the kidney and liver as the principal sources of the two main VD metabolites are included target organs for Cd and Pb toxicity, diverse studies have been performed in this domain in order to determine probable associations and mechanisms.

Cd is an environmentally widespread toxic metal with a long biological half-time in organs. The kidney, liver, bone, and cardiovascular system are the main targets for Cd toxicity (Roe, 1993). According to a series of human studies performed in the Cd-polluted areas of Japan, exposure to environmental Cd causes perturbations in VDES (Nogawa et al., 1990; Nogawa et al., 1987; Tsuritani et al., 1992). The most severe form of Cd intoxication can be seen in patients with a bone disease called itai-itai. These patients suffer from a painful bone damage characterized by a combination of osteomalacia and osteoporosis, two VDD-associated disorders. Nogawa et al. found decreased serum $1,25(OH)_2D$ levels in itai-itai disease patients and Cd-exposed subjects with kidney damage compared with non-exposed individuals (Nogawa et al., 1987). As mentioned, the kidney is the main producer of circulating $1,25(OH)_2D$; therefore, disturbance in its function can essentially influence biological responses throughout the body via the deficiency of the active form of VD. Reducing activity of enzyme involved in hydroxylating 25(OH)D to $1,25(OH)_2D$ has been proposed as a possible mechanism (Alfvén et al., 2000). The first toxic manifestation reported in all human exposure to cadmium is renal tubular dysfunction. There is growing evidence suggesting that kidney damage is the most likely pathway by which an internal VDD could be occurred, which in turn results in bone damage through a reduced level of calcium (Kido et al., 1989). Tsuritani and colleagues suggested that this Cd-exposure-derived consequence could lead to the impaired activation of VD as well as an increase in the PTH level (Tsuritani et al., 1992). VDD is certainly present in individuals with very low levels of total S-25(OH)D accompanied by hyperparathyroidism, hypocalcemia, or low bone mineral density (BMD) (Powe et al., 2013). Among Cd-exposed women, a significant correlation between serum $1,25(OH)_2D$ and PTH levels with indices of renal tubular dysfunction has been revealed (Tsuritani et al., 1992). In an experimental study, 30 three-old-months female rats have exposed to cadmium chloride in a dose of 50 mg Cd/l in drinking water for 3 months. Results provided clear evidence that long-term exposure to cadmium chlorine would inhibit renal 1-α-hydroxylase activity, which resulted in reduction of the serum $1,25(OH)_2D_3$ level (Youness et al., 2012). In a similar study, Brzoska and colleagues depicted that low lifetime exposure to $CdCl_2$ can affect the metabolism of calciotropic hormones, such as $1,25(OH)_2D$ in female rats. Exposure to 1 mg Cd/l in drinking water for 24 months, resulted in a significant depression in the serum 25(OH)D and $1,25(OH)_2D$ by 50 and 31%, respectively. The 55% decrease in the kidney mitochondrial fraction in the exposed rats bolstered this theory that disorders in VD metabolism caused by exposure to Cd are related to the kidney functional status (Brzóska and Moniuszko-Jakoniuk, 2005). It seems that the decreased renal production of $1,25(OH)_2D$ is proportional to the progression of Cd-induced renal tubular dysfunction (Keiko and Minoru, 1991). In agreement with information provided by human and animal studies, WHO suggests that Cd-induced bone effects may be mediated by renal tubular dysfunction, which in turn leads to reduced activation of VD and decreased calcium absorption from the gut (Organization, 2000; Roe, 1993).

The renal damage due to environmental Cd exposure can be lead to elevated urinary levels of DBP as well (Kasuya, 2000). DBP plays a critical role at VDES as it binds the principal VD metabolites (25(OH)D and $1,25(OH)_2D$). DBP acts to bind and transport VD throughout the body. DBP binds 88% of serum 25(OH)D and 85% of serum $1,25(OH)_2D$. DBP is also important for the renal activation of 25(OH)D to $1,25(OH)_2D$(White and Cooke, 2000). Uchida et al. investigated the relationship between urinary DBP levels and markers of renal tubular dysfunction in the residents of a high Cd-polluted area (Cd group) compared with people settled in the low Cd-polluted region (reference group). They observed significantly higher levels of urinary DBP among highly Cd-exposed individuals. Both Cd and reference groups showed remarkable positive correlations between urinary level of DBP and renal tubular dysfunction (Uchida et al., 2007). As urinary loss of DBP may decrease the capacity for reabsorption and activation of VD in proximal tubules, such deterioration of renal tubular function can justify the low level of $1,25(OH)_2D$ under exposure to Cd (Berg, 1999). A perturbation in the conversion of 25(OH)D to $24,25(OH)_2D$ and $1,25(OH)_2D$ has been reported under the situation of increased blood and urinary Cd and blood Pb among smelter workers (Chalkley et al., 1998). In several disorders, striking evidence distinguishes the role of Pb intoxication in the daily intakes of VD and the concentrations of hydroxylated metabolites of cholecalciferol (Anetor et al., 1999; Arbuckle et al., 2016; Dongre et al., 2013; Edelstein et al., 1984; Mazumdar et al., 2017; Rahman et al., 2018; Szabo et al., 1991).

Because of the extensive use of lead in different industries, most of the existing Pb in our environment originates from human activities. Pb is an endocrine modulator in human populations and is considered as one of the risk factors of VDD (Dyer, 2007; Rahman et al., 2018). There is adequate evidence that depicts lead poisoning would have similar effects with Cd on the metabolic pathway of VD, especially in children (Box et al., 1981; Chang et al., 2014; Mahaffey et al., 1982; Rosen et al., 1980; Sorrell et al., 1977). Rosen and colleagues observed a significant negative correlation between blood lead level (BLL) and serum $1,25(OH)_2D$ among lead-burdened children. In one to five-year-old children with increased blood concentration of Pb (33–120 μg/dl), serum concentrations of $1,25(OH)_2D$ were decreased to levels seen in patients with hypoparathyroidism and metabolic bone disorders. The level of active form of VD turned to the normal level when BLL declined to < 30 μg/dl (Rosen et al., 1980). In a similar study performed by these researchers on 177 1–16-year-old individuals, remarkable

negative association ($r = -0.88$) was obtained between serum $1,25(OH)_2D$ levels and the concentrations of blood lead over the entire range of BLL (12 to 120 μg/dl). Adolescents aged between 11 and 16 years had serum $1,25(OH)_2D$ levels higher than those observed among children 10 years old or younger (Mahaffey et al., 1982). Such a negative correlation was found between BLL and plasma 25(OH)D below 8.32 ng/ml in Asian children (Box et al., 1981). It has been suggested that further susceptibility of children to Cd and Pb could be attributed to the gradual process of maturity in kidney from fetal period to adulthood (Chalkley et al., 1998). An epidemiological study in China investigated the prevalence of VDD and insufficiency related to BLL. This cross-sectional study performed by Chang et al. confirmed the negative correlation between 25(OH)D and BLL ($r = -0.216$, $P < 0.001$). After multivariable adjustment, increasing child age, especially between 8 and 14 years (OR = 18.29; 95% CI 10.14, 32.99; $P < 0.001$) and BLL (OR = 1.01; 95% CI 1.00, 1.02; $P = 0.045$) were the significant predictors of 25(OH)D deficiency and insufficiency (Chang et al., 2014). In fact, this study affirmed some relationship between VD status and age-related accumulation of Pb in children.

It is of interest that intake of VD could be modulated by exposure to lead. Through a cohort of 2001 pregnant women, it has been shown that VD intake is negatively associated with maternal blood Cd, Pb, and manganese (Mn), as well as cord blood Pb. Regression analysis demonstrated that higher intake of Ca and VD can be correlated with lower maternal Pb and Cd concentration (Arbuckle et al., 2016). Sorrel et al. reported an interesting chain of correlations among High BLL, 25(OH)D level, and VD intake that may be a rational justification for the decreased serum levels of hydroxylated metabolites of cholecalciferol under exposure to Pb. High BLL (≥60 μg/l) was associated with the declined level of 25(OH)D in lead-burdened children (18 ± 1 ng/ml) versus controls (32 ± 1 ng/ml). On the other hand, they figured out a positive correlation between VD intake and S-25(OH)D as the high blood Pb group had lower mean daily intakes of VD (210 ± 17 International Unit (IU) vs. 325 ± 20 in controls, $P < 0.001$) (Sorrell et al., 1977). As a result, a disturbance in the intake of VD can affect its serum and kidney hydroxylated metabolites.

Recently, experimental data verified the destructive role of Pb exposure in the metabolism of VD by affecting the expression of the involved enzymes. For the first time, the impact of Pb on the serum levels of VD metabolites, VD metabolizing enzymes (25-hydroxylase and 1α-hydroxylase), and VDR was observed in Wistar rats exposed to 0.2% Pb-acetate via their dams' drinking water from post-natal day (PND) 1 to 21 and directly in drinking water until PND30. S-25(OH)D markedly dropped at both PND21 and PND30, whereas $1,25(OH)_2D$ was decreased ($P < 0.05$) only at PND21 in the Pb-exposed rats. Additionally, renal 1-α-hydroxylase was decreased by Pb only at PND21 ($P < 0.05$) but the brain 1α-hydroxylase was not influenced. Hepatic expression of 25-hydroxylase was substantially reduced at PND21 (Rahman et al., 2018). In human studies, a dramatic decrease of $25(OH)D_3$ serum level has been reported in jewelry workers compared with controls ($P < 0.0001$) (Mazumdar et al., 2017), and of $1,25(OH)_2D_3$ serum level in battery manufacture workers ($P < 0.01$) (Dongre et al., 2013).

3.4.2.2. Uranium and cesium. U is an alpha-emitting heavy metal occurring naturally in the earth's crust. Mining, energy industries, and nuclear accidents are the main risk of exposure to depleted and enriched uranium (DU and EU, respectively). Unfortunately, during the last decades, environmental concentrations of U have been increasing because of the growing use of this radionuclide in civil and military applications. Ingestion, skin penetration, and inhalation are the ways by which U can enter the body. Although a wide range of organs can be targeted by chemical and radiological toxic impacts of U, its major health effect is chemical kidney toxicity (ENDS, 2011).

In the case of U, according to the information provided by in vivo studies, it also appears that disrupting of renal production of VD is the underlying mechanism that interferes with VDES (Tissandié et al., 2008; Tissandie et al., 2007; Tissandie et al., 2006b; Yan et al., 2011). To investigate the impacts of DU on vitamin D_3 metabolism, Tissandie and colleagues chronically exposed rats to DU through drinking water at 40 ml/l for 9 months. For the first time, this study demonstrated that DU decreased plasma level of $1,25(OH)_2D_3$ and VD receptor expression in the kidney, resulting in the modulation of CYP24A1 expression and VD target genes in calcium homeostasis. In addition to a small decrease of $25(OH)D_3$ in plasma, low level of CYP27A1 (the gene encoding $25(OH)D_3$) has been observed in the brain of DU-exposed rats compared to the controls (Tissandie et al., 2007). In a similar study, the significant reduction of 1α-hydroxylase in the kidney of rats has been reported under chronic exposure to DU (Yan et al., 2011). Likewise, the chronic exposure to EU influences both mRNA and protein expression of renal nuclear receptors involved in the metabolism of VD (Tissandié et al., 2008). Consistent with findings obtained from experimental investigations on rats, epidemiological studies on the effects of DU exposure on a cohort of Gulf War veterans described elevated urinary levels of calcium and altered serum levels of PTH and $1,25(OH)_2D_3$ among DU-exposed soldiers (McDiarmid et al., 2011; McDiarmid et al., 2008). Hence, disturbance in renal functions related to VDES is expectable under short- or long-term exposure to environmental DU and EU.

The explosion of Chernobyl nuclear power plant was a disaster that released ^{137}Cs in the environment and imposed serious health consequences on the populations of contaminated areas, mainly through the food consumption. This radioactive metal is formed in the fission nuclear of fissionable isotopes in nuclear reactors and weapons. Chronic contamination by ^{137}Cs can impair the liver metabolism of cholesterol, a precursor for the biosynthesis of steroid hormones, such as VD (Souidi et al., 2006). Tissandie et al. designed a research to explore the biological effects of chronic exposure to a post-accidental dose of ^{137}Cs on VD metabolism in liver, kidney, and brain. For this purpose, they encountered rats to the radioactive metal through drinking water for 3 months at a dose of 6500 Bq/l (approximately 150 Bq/rat/day), a similar concentration ingested by the people residing in contaminated territories in the former Union of Soviet Socialist Republics countries. Besides an insignificant decline in $25(OH)D_3$ and a drastic decrease in $1,25(OH)_2D_3$ (53%, $P = 0.02$) in plasma, CYP2R1 (the key gene encoding $25(OH)D_3$) mRNA level (20%, $P < 0.05$) has exhibited a noticeable drop in plasma level and brain. Nonetheless, the expression level of CYP2R1 in the liver was increased by 40% ($P < 0.05$). CYP27B1 mRNA level was declined in the brain by 20% ($P < 0.05$) as well (Tissandie et al., 2006a). This research group continued their metabolic studies on ^{137}Cs. As children are known to be the most susceptible group for VD metabolism disorders, effects of ^{137}Cs on VD biosynthetic pathway were investigated in newborn rats. The experiments were performed in 21-day-old male offspring of dams exposed to ^{137}Cs under similar conditions with the previous study but during the lactation period. Declined expression levels of CYP2R1 and CYP27B1 (−26 and −39%, respectively, $P < 0.01$) were reported in liver and kidney (Tissandie et al., 2009). Further, a significant increase of $1,25(OH)_2D_3$ and an unaffected level of $25(OH)D_3$ (similar to the previous study) has been reported in that study.

3.4.3. EDCs

Rapidly increasing evidence suggests that environmental pollutions, particularly POPs possess an offensive capability to disrupt endocrine systems. Biological and environmental accumulation, lipophilicity, hydrophobicity, and resistance to environmental degradation are common traits of POPs, which include polychlorinated biphenyls (PCBs), polychlorinated dibenzo-*p*-dioxins (PCDDs), polychlorinated dibenzofurans (PCDFs), and organochlorine (OC) pesticides (Council, 2006). As mentioned above, since hormonally active VD metabolite and PTH have a vital interrelated role in the optimal balance of phosphorous and calcium for regulating bone mineralization, disrupting VD homeostasis may affect skeletal development and bone metabolism (Fig. 2). In fact, $1,25(OH)_2D$-simulated intestinal absorption and renal reabsorption of phosphate and

calcium induces bone mineralization. Lowering the active metabolite of VD bring about disturbances in bone mineralization and subsequently progressive bone loss (Holick, 2006). There are a couple of field and animal investigations showing the perturbations in VDES and decreased serum levels of 25(OH)D and $1,25(OH)_2D$ under exposure to POPs, especially PCBs and Dichlorodiphenyltrichloroethane (DDT) (Alvarez-Lloret et al., 2009; Fletcher et al., 2005; Ju et al., 2012; Lilienthal et al., 2000; Routti et al., 2008).

In the first study of PCB-induced effects on vitamin D_3 metabolites, serum concentrations of 25(OH)D and $1,25(OH)_2D$ were evaluated in rat dams and offspring after exposure to a mixture of PCB reconstituted based on the pattern of congeners found in human breast milk. Dose-dependent reductions in serum levels of both VD metabolites were observed in both dams and newborns. It should be added that even at the lowest level of exposure (5 mg PCB/kg diet), reductions of $1,25(OH)_2D$ were seen in dams (Lilienthal et al., 2000). Also, it was shown that embryonic exposure to 2,2′,3,3′,4-pentachlorobiphenyl (Arclor1254) have the capability to induce developmental deficits in the zebrafish skeleton subsequent to changes in PTH and VDR expression (Ju et al., 2012). These outcomes suggest that exposure to POPs could play an effective role in the VD metabolism. Non-maternal exposure to POPs generates similar impacts. Through an experiment on Baltic seals, Routti and colleagues perceived that thyroid system and VD are initial targets for PCBs and DDT to disturb bone homeostasis. Gray seals that were exposed to high levels of these chemicals have shown decreased levels of $1,25(OH)_2D$ and thyroid hormones, which were negatively related to hepatic POPs. In accordance with the incorporated information, the authors concluded that contaminant-mediated VD and thyroid disruption might explain the bone lesions observed in the seals (Routti et al., 2008). Similar findings were realized in the case of exposure to dioxin-like PCBs. Using two cutting-edge techniques, namely Fourier transform infrared spectrometry (FTIR), and transmission electron microscopy (TEM), lower degree of mineralization (−8.5%; $P < 0.05$) and undesirable changes in size and crystallinity were detected in the vertebrae of rats exposed to 3,3′,4,4′,5-pentachlorobiphenyl (PCB126) compared with controls (Alvarez-Lloret et al., 2009). According to Norman (Norman, 2008), correct bone mineralization depends on VD-provided balance of calcium and phosphorous; therefore, lower levels of thyroid hormones, and VD (−21%; $P < 0.005$) seen in the rats exposed to PCB126 would potentially contribute in bone dysfunction (Alvarez-Lloret et al., 2009).

Recent epidemiological studies indicate a correlation between reduction of serum VD levels and exposure to POPs (Morales et al., 2013; Yang et al., 2012). In a Spanish population-based cohort, cross-sectional association of S-$25(OH)D_3$ (measured by gas chromatography) with the serum concentration of eight POPs (measured by high-performance liquid chromatography) were examined in 2031 pregnant women. Multivariate regression models disclosed an inverse linear relationship between PCB180 and S-$25(OH)D_3$ in which higher PCB180 levels were associated with lower $25(OH)D_3$ level: quartile Q4 vs. quartile Q1, coefficient = −1.59, 95% CI −3.27, 0.08, P trend = 0.060. A non-monotonic inverse association was also discovered between the sum of predominant PCB congeners (PCB 180, 153 and 138) and $25(OH)D_3$ concentration: coefficient (95% CI) for quartile Q2 vs. Q1 [−0.50 (−1.94, 0.94)], quartile Q3 vs. Q1 [−1.56 (−3.11, −0.02)] and quartile Q4 vs. Q1 [−1.21 (−2.80, 0.38)], P trend = 0.081 (Morales et al., 2013). The role of POPs in the pathogenesis of chronically metabolic disorders has been ascribed to their endocrine disrupting features. Importantly, some of the mentioned diseases have been associated with VDD. The first human study that linked the OC pesticides and S-25(OH)D in human was performed by Yang and colleagues. They sought the association between seven OC pesticides and S-25(OH)D in the 1275 subjects aged > 20 years. Of measured pesticides, *p,p′*-DDT ($\beta = -0.022$, $P < 0.01$), *p,p′*-DDE ($\beta = -0.018$, $P = 0.04$), and β-HCH ($\beta = -0.022$, $P = 0.02$) showed significant inverse associations with S-25(OH)D levels (Yang et al., 2012). Based on the found inverse association between PCBs and OC pesticides, it can be inferred that background exposure to these chemicals may lead to lower level of serum VD and probably VDD.

There is scarce human evidence of the destructive role of two main endocrine disrupting agents, namely phthalate and BPA, in VDES (Erden et al., 2014; Johns et al., 2017; Johns et al., 2016). Phthalate and BPA are broadly utilized for the production of a vast range of industrial and consumer products. These environmental chemicals have been extensively detected in the U.S. population. Johns et al. assessed the relationship between phthalate and BPA and VD by data obtained from a cross-sectional study with 4724 adults (aged ≥20 years). They reported an inverse association between total S-25(OH)D and urinary levels of di (2-ethylhexyl) phthalate (DEHP) metabolites in the overall population and urinary BPA only in women (Johns et al., 2016). This finding was consistent with the remarked negative correlation between serum BPA and S-25(OH)D reported among 128 patients with obstructive sleep apnea syndrome (OSAS) (Erden et al., 2014). Johns and colleagues evaluated the relationship between urinary phthalate metabolites and BPA and circulating total 25(OH)D in a large prospective cohort of pregnant women with 477 participants. Repeated measures of urinary DEPH metabolites and mono-3-carboxypropyl phthalate (MCPP) were negatively correlated with total S-25(OH)D levels. A non-significant inverse association was detected in the overall population analysis between urinary and total 25(OH)D (Johns et al., 2017).

Carbon tetrachloride (CCl_4), as a hepatotoxic solvent, is capable of disrupting VDES. For the first time, Nussler et al. reported some disturbances in the expression of genes involved in the VD metabolism. The hepatic expression levels of CYP2R1, CYP27A1, and VD-binding protein GC have significantly reduced in C27B16/N mice after 6-week treatment with CCl_4. They have also reported a meaningful increase in 7-dehydrocholesterol reductase (DHCR7) gene expression in the liver (Nussler et al., 2014). Since there is a direct correlation between the expression of genes CYP2R1, CYP27A1, DHCR7 and GC with S-25(OH)D levels in healthy populations (Bu et al., 2010; Wang et al., 2010), it can be inferred that exposure to CCl_4 is capable of significantly decreasing VD levels.

3.4.4. Contributions of environmental contaminations in most likely mechanisms toward VDD

According to the conducted studies on the role of exposure to environmental pollutants in VDD until now (summarized in Table 1), whether human or animal, a variety of mechanisms have been proposed to interfere in VDES resulting in VD deficiency.

Sunlight exposure accounts for > 90% of VD production in human beings (Hoseinzadeh et al., 2018). Despite the stated evidence, air pollution might be an ignored risk factor while it is important for dysregulating VDES at the early stage. As shown in the Fig. 3, air pollutants could change the VD status directly and indirectly. Outdoor air pollutants, especially ozone and PMs can limit UVB photons reaching the ground through absorption of these sunlight's radiations. Thus, they can affect the cutaneous production of precholecalciferol and finally vitamin D_3. Moreover, air pollution in certain situations may discourage people to engage in daily outdoor activities. This can synergistically, and indirectly decrease the cutaneous production of VD.

Increases of hypovitaminosis D in populations, while benefiting from enough dietary intakes of VD, makes environmental risk factors, such as air pollution a culprit. Overall, increases in air pollutants concentrations, may diminish sunlight rays reaching the skin and consequently lessen the cutaneous production of vitamin D_3. Recent studies reported that usage of sunscreens with higher sun protection factor (SPF) in a regular basis could affect cutaneous production of VD among those individuals that are living in air-polluted areas with sunny climates (Faurschou et al., 2012; Libon et al., 2017).

Other studies have reported that exposure to Cd and Pb could lead to damages to kidney, especially renal tubular dysfunction and consequently impair bone homeostasis (Dongre et al., 2013; Keiko and

Table 1
The effects of environmental contaminants on VDES.

Authors/country/study type	Participants/age	Exposure	Dose/period	Key result	Key conclusion
Calderón-Garcidueñas et al. (2015)/Mexico/human	54 children and 26 controls/aged 11.17 ± 3.2 years	Air pollution ($PM_{2.5}$)	$PM_{2.5}$ above standard value	25(OH)D < 30 in 46% 25(OH) D was 21–29 in 41%	Mexico City normal weight children exposed to high concentrations of $PM_{2.5}$ showed VDD versus controls in low-polluted areas
Kelishadi et al. (2014)/Iran/cross-sectional	100 children/aged 4–10 years	Air pollution	AQI: median: 144 IQR: 125–177	VD deficiency and insufficiency were detected in 37.9% and 46.3% of children, respectively.	AQI was inversely associated with S-25(OH)D level.
Calderón-Garcidueñas et al. (2013)/Mexico/human	20 children aged (6.17 ± 0.63 years) and 15 controls (6.27 years ± 0.76 years)	Air pollution (PM and O_3)	PM and O_3 above standard value	Severe deficiency of VD in MCMA children (389 ± 141) IU while the daily requirement is 600 UI.	Highly polluted air with O_3 and PM levels above standard values decreases absorbed UV light and spent time outdoors, which synergistically increases VDD.
Baïz et al. (2012)/France/human	375 mother-newborn pairs	Air pollution (NO_2 and PM_{10})	–	25(OH)D levels decreased by 0.15 U and 0.41 U for a 10 μg/m^3 increase in NO_2 and PM_{10} pregnancy levels	Gestational exposure to ambient urban air pollution, especially during late pregnancy may contribute to lower VD levels in offspring.
Hosseinpanah et al. (2010)/Iran/cross-sectional	100 women from Tehran and 100 from Gazvin/20–55 years	Air pollution in Tehran (high-polluted city) vs Gazvin (low polluted city)	–	Mean ± SD of S-25(OH)D: In Tehran: 7 ± 13 In Gazvin: 11 ± 18	Living in a polluted area plays a significant independent role in VD deficiency.
Manicourt and Devogelaer (2008)/Belgium/cross-sectional study	38 from urban residents and 47 from rural residents/51–81 years	Air pollution (O_3)	Urban inhabitants were exposed to O_3 levels 3 times higher than rural residents	Prevalence of S- 25(OH)D < 30: In Urban area: 32 of 38 In Rural area: 18 of 47	Air pollution may be a risk factor for hypovitaminosis D.
Agarwal et al. (2002)/India/cross-sectional	26 infants from Mori Gate and 31 form Gurgaon/9–24 months	Air pollution Mori Gate (high pollution area) and Gurgaon (less pollution area)	–	Mean S-25(OH)D: In Mori Gate: 12.4 ng/ml In Gurgaon: 27.1 ng/ml	Children living in areas of high atmospheric pollution are at risk of developing VD deficiency rickets.
Arbuckle et al. (2016)/Canada/cohort	2001 pregnant women/aged ≥18 years	Cd, Pb, Mn and Hg	The metals were measured in maternal blood from the 1st and 3rd trimesters, umbilical cord blood, and infant meconium.	VD intake was significantly associated with lower maternal blood Cd, Pb, and Mn, and lower Pb in cord blood in the regression analysis.	Higher Ca and VD intake can be associated with lower maternal blood Pb and Cd concentrations.
Youness et al. (2012)/Egypt/animal	30 three-months-old female Sprague Dawley rats	Cd chloride	50 mg Cd/l in drinking water for 3 months	Cd exposure resulted in significant reduction in serum $1,25(OH)_2D_3$ level in exposed rats.	Long-term exposure to cadmium chloride produced marked abnormalities in bone biomarkers and increasing risk of fracture.
Uchida et al. (2007)/Japan/human	Cd group: 8 women including 5 itai-itai patients; mean age: 83.5 ± 9.67 years Reference group: 21 age-matched female subjects	Environmental Cd	Cd group lived in a Cd-polluted area for > 50 years and Ref. group lived in the low-Cd-polluted area	DBP level in Urine (μg/gCr): In Cd group: 23,000 (10,200–40,600) In Ref. group: 422 (215–1200)	The increase of DBP in urine may be linked to renal tubular dysfunction and possibly bone lesions in the inhabitants of Cd-polluted areas.
Brzóska and Moniuszko-Jakoniuk (2005)/Poland/animal	20 female Wistar rats Exposed group: 10 Controls: 10 Age: 3 weeks old	$CdCl_2$	1 mg Cd/l in drinking water for 24 months	1. Decrease in the serum concentrations of 25(OH)D and $1,25(OH)_2D$. 2. The concentration of $1,25(OH)_2D$ in the mitochondrial fraction of the kidney of Cd-exposed rats was lower by 55% compared to the controls. 3. Serum level of $1,25(OH)_2D$ was statistically significantly correlated (positively) with the serum 25(OH)D level and the kidney $1,25(OH)_2D$ level. 4. A positive relationship observed between 25(OH)D in serum and $1,25(OH)_2D$ in kidney.	The low lifetime exposure to Cd affects the metabolism and proper function of calciotropic hormones. The disorders in VD metabolism due to the exposure to Cd are related to the kidney functional status.

(*continued on next page*)

Table 1 (*continued*)

Authors/country/study type	Participants/age	Exposure	Dose/period	Key result	Key conclusion
Chalkley et al. (1998)/ London/human	59 smelter workers	Cd and Pb	Occupationally exposed to Pb and Cd.	1. Plasma $25(OH)D_3$ was negatively correlated with urinary Cd. 2. Exposure to Cd alone decreased the concentrations of $1,25(OH)_2D_3$ and $24,25(OH)_2D_3$.	Cd and Pb interact with renal mitochondrial hydroxylases of the vitamin D_3 endocrine complex.
Tsuritani et al. (1992)/ Japan/human	30 males and 44 females in the exposed group and 24 men and 48 women in the control group/ 50 years and above	Environmental Cd	The exposed group were from Cd-polluted area and control group from the non-Cd-polluted area	Serum VD decreased in the exposed group, significantly in women.	Renal damage due to Cd exposure induces the impairment of VD metabolism.
Keiko and Minoru (1991)/ Japan/human	11 women/60–73 years	Environmental Cd	–	The levels of S-25(OH)D were low-normal with a mean of 13 ± 5.0 ng/ml in 11 subjects.	Renal production of $1,25(OH)_2D$ decreases with progression of cadmium-induced renal tubular dysfunction.
Nogawa et al. (1990)/ Japan/human	10 exposed subjects and 5 controls	Environmental Cd	–	Serum 24,25 $(OH)_2D$ and $1,25(OH)_2D$ in Cd-exposed subjects increased compared to controls.	Cd initially disturbs hydroxylation from 25(OH)D to $24,25(OH)_2D$ and then disturbs hydroxylation from 25(OH)D to $1,25(OH)_2D$.
Nogawa et al. (1987)/ Japan/human	5 itai-itai patients 36 (10 men and 26 women) exposed, and 17 (6 men and 11 women) non-exposed individuals/over 59 years	Environmental Cd	Exposed group and itai-itai patients were from Cd-polluted area and control group from the non-Cd-polluted area	Serum $1,25(OH)_2D$ levels were lower in itai-itai disease patients and Cd-exposed subjects than in non-exposed subjects.	Cd induces kidney damage, which in turn leads to a disturbance in VD and parathyroid hormone metabolism.
Rahman et al. (2018)/ Kuwait/animal	Newborn Wistar rat pups Pb-exposed: 37 Control group: 38	Pb-acetate	0.2% Pb-acetate via their dams' drinking water from PND 1 to 21 and directly in drinking water until PND30.	PND21-25(OH)D Pb-exposed group: 58.3 ± 14.3 Control group: 81.25 ± 18.75 PND30-25(OH)D Pb-exposed group: 67.5 ± 16 Control group: 80.5 ± 15.75 PND21-$1,25(OH)_2D$‡ Pb-exposed group: 361.5 ± 83.6 Control group: 428.8 ± 132.8 PND30-$1,25(OH)_2D$ Pb-exposed group:379.7 ± 108.1 Control group: 416.9 ± 129.1	Pb interferes with VD metabolism by affecting the expression of its metabolizing enzymes.
Mazumdar et al. (2017)/ human/Bangladesh	Jewelry workers: 47 Age: 29–65 years Control group: 42 Age: 32–62 years	Fumes and dust of Pb	Jewelry workers were employed full time (average 8–12 h/day), for 10–25 years and exposed to Pb.	S-25(OH)D Jewelry workers: 12.8 ± 3.9 Control group: 32.6 ± 9.6	Vitamin D_3 significantly decreased in the study group. It may be due to the inhibition of 1α-hydroxylase enzyme in renal tubules.
Chang et al. (2014)/a cross-sectional and 1-year retrospective study/China	1218 children/6 months to 14 years old	Environmental Pb	–	There was a negative correlation between 25(OH)D concentration and BLL.	The prevalence of 25(OH)D deficiency and insufficiency was associated with BLL and age.
Dongre et al. (2013)/ human/India	Battery manufacture workers Exposed groups: 3 Age: 30 years Control group Age: 30 years	Pb acid battery	Group I: 1 to 5 years Pb exposure Group II: 6–10 years Pb exposure Group III: > 10 years Pb exposure	1. Percentage change of Pb-B and Pb-U in three groups of workers was observed with respect to controls. 2. Significantly decreased total calcium, ionized calcium, phosphorus, VD and bone mineral density were observed in battery manufacture workers as compared to control group	The absorption of lead is more in these workers, which adversely affects blood pressure, disturbs calcium and phosphorus metabolism. This further impairs mineralization of bone resulting in decreased bone mineral density observed in these workers.
Anetor et al. (1999)/ Nigeria/human	86 men	Pb	Participants were occupationally exposed to Pb.	$1,25(OH)_2D_3$ was significantly lower in lead workers than in the control population ($P < 0.001$).	Occupational lead exposure decreases the serum level of serum $1,25(OH)_2D_3$.

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Table 1 (*continued*)

Authors/country/study type	Participants/age	Exposure	Dose/period	Key result	Key conclusion
Szabo et al. (1991)/ Germany/animal	Male Wistar Kyoto rats Exposed rats: 10 Control group: 10	Pb acetate	1% Pb acetate in drinking water for 10 weeks (short-term study) OR 0.001–1% Pb acetate for 24 weeks (long-term study)	Circulating $1,25(OH)_2D_3$ (177 ± 10.9 vs. 232 ± 18.9 Pmol/l) were significantly decreased.	Secondary hyperparathyroidism was associated with Pb, and presumably caused by, hypocalcemia and low $1,25(OH)_2D_3$ levels, in experimental Pb intoxication.
Edelstein et al. (1984)/ USA/animal	Chick/one day old	Pb-containing rachitogenic diet	For 2 weeks 1) control 2) 1000 ppm Pb 3) 3000 ppm Pb 4) 6000 ppm Pb.	The concentration of the three hydroxylated forms, namely, $25(OH)D_3$, $24,25(OH)_2D_3$ and $1,25(OH)_2D_3$ decreased significantly.	Ingestion of lead impairs growth and renal production of $1,25(OH)_2D_3$ resulting in lowered circulating and intestinal content of the hydroxylated metabolites of cholecalciferol.
Mahaffey et al. (1982)/ human/USA	177 human subjects ages 1 to 16 years	Environmental Pb	–	–	A significant negative association was observed between serum $1,25(OH)_2D$ levels and blood lead concentrations over the entire range of blood lead levels, 12 to 120 µg/dl.
Box et al. (1981)/human/ UK	78 Asian children	Environmental Pb	–	–	A negative correlation was found between S-25(OH)D and BLL.
Rosen et al. (1980)/ human/USA	Group I: 15 (2.9 ± 0.6) Group II: 18 (3.3 ± 0.7) Group III: 12 (3.1 ± 0.1)	Pb	BLL(µg/dl) Group I (control): 18 ± 1 Group II: 42 ± 2 Group III: 74 ± 8	S-25(OH)D Group I: 27 ± 2 Group II: 28 ± 1 Group III: 20 ± 1 Serum $1,25(OH)_2D$ Group I: 33 ± 2 Group II: 20 ± 1 Group III: 14 ± 2	1. S-25(OH)D levels were significantly lower in Group III. 2. Reduction in the serum $1,25(OH)_2D$ concentration appears to be a sensitive index of increased levels of lead in the blood.
Sorrell et al. (1977)/USA/ human	Children/1–6 years	Environmental Pb	BLL(µg/dl) Group I (control) ≤ 29 Group II: 30–59 Group III ≥ 60	1. Group III had a significantly lower daily intake of VD (210 ± 17 IU vs. 325 ± 20 in controls, $P < 0.001$). 2. S-25(OH)D was significantly lower in group III (18 ± 1) compared to groups I and II (32 ± 1.0 and 30 ± 1) ($P < 0.001$). 3. S-25(OH)D was correlated positively and significantly with VD intake in all groups.	1. The concentration of S-25(OH)D was a function of primarily VD intake. 2. High BLL (≥60 µg/dl) in children were associated with decreased quantities of 25(OH)D in serum and lower mean daily intakes of both calcium and VD.
Yan et al. (2011)/animal/ China	Five group of male Sprague-Dawley rats 1: depleted uranium (DU): none 2: Ta 0.3 g; DU 0.1 g 3: Ta 0.2 g; DU 0.2 g 4: Ta 0.1 g; DU 0.3 g 5: Ta none	Animals received implantation of DU and tantalum (Ta).	The rats in the experimental groups were exposed to DU for 3, 6 or 12 months	1α-Hydroxylase activity in the kidney was decreased after 3 months (27.2% at the medium dose DU group, 33.4% at the high dose DU group)	Chronic DU exposure could induce renal damages and inhibit the synthesis of the biologically active form of VD.
Tissandié et al. (2008)/ animal/France	20 Sprague-Dawley male rats/ 12 weeks old EU-exposed group: 10 Control group: 10	Rats were exposed to EU in their drinking water.	Concentration of 40 mg/l (1 mg/rat day)/9 months	VDR and RXRα showed a low expression in the kidney.	Chronic exposure to EU affects both mRNA and protein expressions of renal nuclear receptors involved in VD metabolism.
Tissandie et al. (2007)/ animal/France	20 Sprague-Dawley male rats/ 12 weeks old DU-exposed group: 10 Control group: 10	Rats were exposed to DU in their drinking water.	Concentration of 40 mg/l (1 mg/rat day)/9 months	1. In exposed rats, $1,25(OH)_2D_3$ plasma level was significantly decreased. 2. In the kidney, a decreased gene expression was observed for CYP24A1, VDR, and RXRα. 3. In the brain, lower levels of messengers were observed for CYP27A1.	DU affects both the VD active form $1,25(OH)_2D_3$ level and the VD receptor expression.

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Table 1 (*continued*)

Authors/country/study type	Participants/age	Exposure	Dose/period	Key result	Key conclusion
Tissandie et al. (2006a, b)/ animal/France	16 10-week-old male Sprague–Dawley rats DU-exposed group: 8 Control group: 8	DU	Intragastric administration of DU (204 mg/kg)	CYPs, VD, and PTH plasma levels were altered in DU-exposed rats.	DU acute contamination modulates both activity and expression of CYP enzymes involved in VD metabolism in liver and kidney.
Tissandie et al. (2009)/ animal/France	9 Sprague- Dawley female rats/ 12 weeks old ^{137}Cs-exposed group: 4 Control group: 5	^{137}Cs	Drinking water at a dose of 6500 Bq/l (150 Bq/rat/day) for 21 days	Decreased expression levels of CYP2R1 and CYP27B1 (−26 and −39%, respectively) and RXRα were measured in liver and kidney of offspring respectively.	Exposure to post-accidental doses of ^{137}Cs induces the alteration of VD metabolism.
Tissandie et al. (2006a, b)/ animal/France	20 Sprague–Dawley male rats/ 12 weeks old ^{137}Cs-exposed group: 10 Control group: 10	^{137}Cs	Drinking water at a dose of 6500 Bq/l (150 Bq/rat/day) for 3 months	1. 40% increase in the expression level of CYP2R1 in the liver of exposed rats. 2. Significant decrease (53%) of $1,25(OH)_2D_3$ plasma level. 3. 20% decrease in CYP2R1 mRNA level in the brain of exposed rats. 4. The expression level of CYP27B1 increased after ^{137}Cs contamination.	Chronic exposure with post-accidental doses of ^{137}Cs affects Vitamin D_3 active form level and induces molecular modifications of CYPs enzymes involved in its metabolism in liver and brain.
Souidi et al. (2006)/ animal/France	20 Sprague-Dawley male rats/^{137}Cs-exposed group: 10 Control group: 10	^{137}Cs	Drinking water at a dose of 6500 Bq/l (150 Bq/rat/day) for 3 months	34% increase in CYP27A1 activity in exposed rats' liver.	Chronic long-term exposure at low-level of ^{137}Cs may evolve into lipid disorder.
Johns et al. (2017)/cross-sectional study/USA	477 pregnant women	BPA and phthalate	–	1. An IQR increase in urinary mono-3-carboxypropyl phthalate (MCPP) was associated with a 4.48% decrease in total 25(OH)D. 2. Inverse associations between DEHP and 25(OH)D was observed.	Environmental exposure to phthalates and/or BPA disrupt circulating VD levels in pregnancy.
Johns et al. (2016)/cross-sectional study/USA	Adult population Age ≥ 20 years	BPA and phthalate	–	1. The significant inverse relationship for the molar sum of DEHP metabolites was associated with total 25(OH)D. 2. A statistically significant inverse relationship between BPA and 25(OH)D was revealed in women, but not in men.	Environmental exposure to Phthalates and BPA may alter circulating levels of total 25(OH)D in adults.
Nussler et al. (2014)/ animal/Germany	C57Bl6/N mice/12 weeks old	CCl_4	Mice: 6-week treatment (1 ml/kg body weight)/3 injections per week	1. The hepatic expression levels of CYP27A1, CYP2R1, and VD-binding protein GC all involved in VD bioactivation were significantly reduced. 2. The hepatic DHCR7 expression was significantly increased. 3. Reduced 25(OH)D level in CCl_4-treated mice was observed.	Six-week CCl_4 treatment induced liver damage in mice resulting an altered VD metabolism with decreased CYP27A1, CYP2R1, VD-binding protein GC and increased DHCR7 hepatic gene expression, resulted in decreased 25(OH)D serum levels.
Erden et al. (2014)/ human/Turkey	128 patients with OSAS Group 1: Control: 43 Group 2: 23 Moderate OSAS patients Group 3: 62 severe OSAS patients	BPA	–	A negative correlation between the 25(OH) D and BPA levels was shown in all of the individuals	OSAS is related to high BPA, PTH, and low VD levels.
Morales et al. (2013)/ cross-sectional study/ Spain	2031 pregnant women	POPs *p,p′*-DDT, *p,p′*-DDE, HCB, β-HCH, and PCB congeners 28, 118, 138, 153 and 180	–	1. An inverse linear relationship was found between serum concentration of PCB180 and circulating $25(OH)D_3$. 2. A non-monotonic inverse relationship was found between the sum of predominant PCB congeners (PCB 180, 153 and 138) and $25(OH)D_3$ level.	Background exposure to PCBs may result in lower $25(OH)D_3$ concentration in pregnant women.

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Table 1 (*continued*)

Authors/country/study type	Participants/age	Exposure	Dose/period	Key result	Key conclusion
Ju et al. (2012)/animal/China	Zebrafish embryos/5 group (90 eggs/group) Group 1: Control Group2:0.01% Methanol Group 3: 0.125 mg/l PCB Group 4: 0.5 mg/l PCB Group 5: 1.0 mg/l	PCB1254	The effects of each concentration were studied at five developmental stages [24, 48, 72, 96 and 120 h post-fertilization (hpf)].	1. The embryos exposed to the higher concentrations of PCBs (0.5 and 1.0 mg/l) displayed obvious skeletal morphological deformities. 2. VDR and PTH mRNA expressions were all affected by PCBs.	Embryonic exposure to PCBs induces developmental deficits in the zebrafish skeleton.
Yang et al. (2012)/cross-sectional study/Korea	1275 subjects aged ≥20	OC pesticides *p,p*9-DDE, *p,p*9-DDT, β-HCH, Dieldrin, Hexachlorobenzene, Oxychlordane, and Transnonachlor	–	*p,p*9-DDT, *p,p*9-DDE, and β-HCH showed significant inverse associations with S-25(OH)D levels.	Background exposure to some OC pesticides leads to VD deficiency in human.
Alvarez-Lloret et al. (2009)/Spain	Sprague–Dawley rats Exposed group: 10 Control group: 10	PCB126	Total dose, 384 μg/kg bodyweight/3 months	Lower levels of thyroid hormones and VD were shown in the exposed group compared with control animals.	The lowering of thyroxin and VD serum levels might be an underlying explanation for the observed effects on bone mineralization.
Routti et al. (2008)/animal/Norway	Gray seals (n = 30) Ringed seals (n = 46)	PCBs and DDT	–	A clear relationship between serum $1,25(OH)_2D$, calcium, phosphate, and thyroid hormone levels and hepatic PCB and DDT load have been found in the gray seals.	Contaminants may depress $1,25(OH)_2D$ levels or lead to hyperthyroidism, which may cause bone resorption.
Fletcher et al. (2005)/animal/Sweden	Long-Evans and Han/Wistar rats/5 weeks old/5 animals per dose groups	2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD)	TCDD once per week by SC injection for 20 weeks at daily doses of 0, 1, 10, 100, or 1000 ng/kg BW/day	$25(OH)D_3$ was decreased only at high dose (100 ng/kg BW/day) in Long-Evans rats where levels were decreased 27% compared to control.	–
Lilienthal et al. (2000)/animal/Germany	80 female rats divided to 4 groups/4–5 weeks old	PCB mixture, which reflects the congener pattern of breast milk. (PCB congeners 28, 77, 101, 105, 126, 169)	From mating to the birth of offspring, rat groups exposed to 0, 5, 20, or 40 mg PCB/kg diet.	1. Gestational exposure reduced serum $1,25(OH)_2D$ level. 2. S-25(OH)D was decreased at the time of delivery. 3. In dams, reductions were seen even at the lowest exposure level used. 4. In offspring, $1,25(OH)_2D$ shoed reductions at weaning in both high-exposure groups. 5. Levels of 25(OH)D were diminished only at the offspring of the highest exposure level.	Exposure to a reconstituted PCB mixture resulted in dose-dependent reductions in serum concentrations of the steroids 25(OH)D and $1,25(OH)_2D$ in rat dams and offspring.

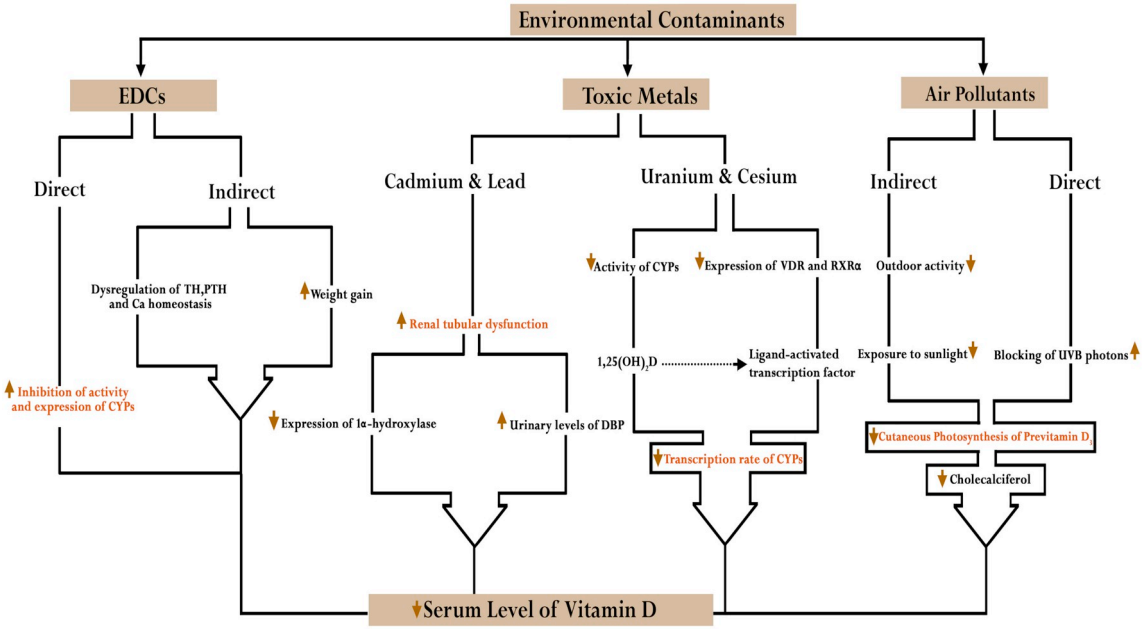

Fig. 3. Possible biochemical pathways that air pollution, toxic metals, and EDCs may lead to VD deficiency (VDD). Decreasing outdoor activity and blocking UVB photons are the two mechanisms that air pollution may lead to the reduction of VD cutaneous production. Increasing renal tubular dysfunction as well as down-regulating the transcription of CYPs are major pathways that heavy metals may initiate to bring about the reduction of VD serum level. EDCs may inhibit the activity and expression of CYPs. They may indirectly cause VDD through weight gain and the dysregulation of TH, PTH, and calcium homeostasis.

Minoru, 1991; Nogawa et al., 1987). Elevated urinary levels of DBP, accumulation of heavy metal in the kidney, and decreased level of $1,25(OH)_2D$ confirm such disturbances (Chalkley et al., 1998; Kido et al., 1989; Uchida et al., 2007). In addition, experimental studies have shown that the impaired renal activation of VD originates from the dysregulation of renal 1α-hydroxylase (Youness et al., 2012). Proximal tubules including their mitochondria are the only sites of $1,25(OH)_2D$ biosynthesis in the kidney (Morgan, 2001). Mitochondria hydroxylases are in charge of the renal conversion of 25(OH)D to $1,25(OH)_2D$ (Youness et al., 2012). Since Cd and Pd exposure are engaged in malfunctioning mitochondria, the interaction of these toxic metals with the resident hydroxylases in renal mitochondria can be an involved mechanism in VDD (Alfvén et al., 2000; Chalkley et al., 1998; Dongre et al., 2013; Mazumdar et al., 2017; Youness et al., 2012). Altogether, the renal tubular dysfunction and in particular the inhibition of the renal 1α-hydroxylase enzyme are the most proposed pathways by which Cd and Pb contribute to VDD (Fig. 3).

In the case of radionuclides U and ^{137}Cs, based on conclusions deduced from in vivo studies in Table 1, exposure to these toxic metals can affect the expression of CYPs enzymes that deal with VD metabolism in liver and kidney, which results in the dysregulation of mineral homeostasis. Such a chain of events could modulate the expression of target genes by affecting the level of vitamin D_3 active form (Tissandie et al., 2006a, b). In fact, disrupting the renal production of VD is an indirect pathway that affects bone development and maintenance. The sustainable and well-balanced production of VD depends on the optimal function of VDES shown in the Fig. 2. In fact, losing the balance between involved factors in VDES influences the serum level of VD metabolites. In target organs of VD including kidney, bone, and intestine, $1,25(OH)_2D$ binds to VDR and forms a heterodimeric complex with the retinoic acid X receptor alpha (RXRα), the receptor for the 9-cis retinoic acid. This complex acts as a ligand-activated transcription factor by altering the transcription rates of target genes, such as CYPs responsible for VD metabolism (Tissandie et al., 2007; Tissandie et al., 2006b). VDR activation by $1,25(OH)_2D$ is a key factor in stimulating the intestinal absorption of calcium and phosphorus, the renal reabsorption of calcium, and other bone-related homeostatic processes. On the other hand, the decreased expression of VDR and RXRα (the principal regulators of CYPs related to the VD metabolism) under exposure to U and ^{137}Cs in animal studies has been reported (Tissandié et al., 2008; Tissandie et al., 2009; Tissandie et al., 2007). Thus, the results obtained by experimental studies can be interpreted that the reduced serum level of $1,25(OH)_2D$ originated from the decreased activity of CYP27B1 and the decreased expression of receptors involved in VD metabolism are two main factors that modulate ligand-activated transcription factor of genes encoding proteins involved in VDES and finally end in VDD. Such procedure is the case with Cd and Pb.

Having background exposure to POPs could be a determinant factor in the pathogenesis of disorders that disrupt endocrine systems. As shown in Table 1, bone-related parameters, as well as thyroid and VD homeostasis, might be disturbed by exposure to EDCs. Vitamin D_3, as a secosteroid, is structurally similar to steroids, such as cholesterol, testosterone, and cortisol. Influence of PCBs on the activity and expression of CYPs isomers, including those that catalyze the metabolism of steroid hormone have been reported. Thus, the disruption of hepatic hydroxylation of cholecalciferol to $25(OH)D_3$ by the metabolites of PCBs containing hydroxyl group is plausible and susceptible to VDD (Morales et al., 2013). Theoretically, the inhibition of activity and expression of CYPs involved in the metabolism of steroid and thyroid hormones through exposure to EDCs depicts that CYPs interrelated to VDES could be probable targets for these chemicals by which POPs exposure-derived VDD observed in human and experimental models can be explained. As an indirect mechanism shown in Fig. 3, disrupting the homeostasis of TH, PTH, and calcium under exposure to POPs leads to chaos in bone metabolism and VDES and consequently the depression of VD level (Alvarez-Lloret et al., 2009; Ju et al., 2012; Routti et al., 2008). Perturbations in endogenous hormonal regulation stemmed from exposure to EDCs could result in weight gain (Elobeid and Allison, 2008; Tang-Péronard et al., 2011) which in turn participates in the hypovitaminosis D (Barrea et al., 2017; Johns et al., 2017; Pereira-Santos et al., 2015).

3.5. Tobacco smoke

Tobacco smoke is a mixture of hazardous chemicals implicated in the pathogenesis of a wide range of diseases. Owing to the presence of toxicologically harmful compounds, such as PAHs, aldehydes, and DDT, the smoke is carcinogen, neurotoxic, and endocrine disrupter (Diamanti-Kandarakis et al., 2009; Smith and Hansch, 2000). As mentioned above, a large number of studies have been conducted on the association of smoking and VDD where it has been one of the determinants of VDD. In this review, we focused on the effect of all types of smoking exposure on VDD, whether active or passive. Growing evidence affirms the disruptive role of this notorious blend in VDES. The incidence and prevalence of hypovitaminosis D among Norwegian adults (Larose et al., 2014), Belgium pregnant women (Vandevijvere et al., 2012), north European elderly women (Andersen et al., 2005), middle-aged and elderly Chinese individuals (Zhen et al., 2015), south Europeans (Cutillas-Marco et al., 2012) young Finnish adults (Lamberg-Allardt et al., 2001), young and middle-aged Greek males (Kassi et al., 2015), elderly Italian women (Isaia et al., 2003) and Spanish newborns (Díaz-Gómez et al., 2007) have been attributed to the exposure to tobacco smoke as an endocrine-disrupting risk factor. Unlike air pollutants, which principally have a significant effect on the photosynthesis of cholecalciferol, based on epidemiological, in vitro and in vivo studies, it appears that smoking effect could be attributed to the enzymatic and hormonal production of the subsequent metabolites.

An increased risk of hypovitaminosis D has been detected among smokers versus non-smokers (odds ratio: 1.8; 95% confidence interval: 1.00–3.35). Smoking also has been correlated negatively with the serum level of PTH ($r = -0.24$; $P < 0.001$) (Cutillas-Marco et al., 2012). There are strong evidences asserting the suppressive role of tobacco smoke in the production of PTH, cholecalciferol, and calcitriol (Brot et al., 1999; Cutillas-Marco et al., 2012; Jorde et al., 2005; Need et al., 2002; Supervia et al., 2006). In light of findings emanated from studies performed in this domain, the decrease of serum level of VD is proportionate to depression in the PTH level in smokers (Need et al., 2002). In fact, the key point is chaos in the interrelated regulation of VD and PTH levels, which results in the disruption of the VD metabolism. Hence, the dysfunctional vitamin D-PTH axis has been proposed as a common impairment, which occurs under tobacco smoke exposure. By using recorded data in the Tromsø study, the serum level of PTH was evaluated in 7896 subjects consisting of smokers and non-smokers. After correcting for confounding variables, the serum PTH levels were significantly lower in smokers compared with non-smokers (3.1 ± 1.4 vs 3.6 ± 1.9 pmol/l in males; 3.1 ± 1.5 vs 3.6 ± 1.8 pmol/l in females (P, 0.001)) (Jorde et al., 2005). Reduced levels of iPTH among smokers have been described in young and old individuals (Gudmundsson et al., 1987; Landin-Wilhelmsen et al., 1995). Moreover, lower intake of VD, decreased levels of S-25(OH)D, and decreased calcium absorption among smokers. Interestingly, one year after smoking cessation, serum levels of PTH have been similar to never smokers (Jorde et al., 2005). Similar results have been obtained in a cross-sectional study conducted by Brot and colleagues. They assessed the effect of smoking on serum VD metabolites and PTH in a cohort of 510 healthy Danish perimenopausal women. In comparison to non-smokers, current smokers (50% of the cohort) had significantly reduced levels of serum $25(OH)D_3$ ($P = 0.02$), $1,25(OH)_2D_3$ ($P = 0.001$), and PTH ($P < 0.001$). They further reported a disruption in the vitamin-PTH system among smokers, which was not explicable via lifestyle factors other than smoking; it was considered a crystal clear explanation for the harmful effect of smoking on osteoporosis in smokers (Brot et al., 1999). It is of interest that S-25(OH)D and osteocalcin have shown an inverse relationship with the number of smoked cigarettes per day in premenopausal women, which may accelerate the rate of bone loss (Hermann et al., 2000). Recently, a Chinese cohort with 612 older men reported a dose-response pattern between lower serum concentrations of VD and greater number of smoked cigarettes per day, longer smoking duration, and more pack-years (Jiang et al., 2016). Such results support the inverse association between VDD and smoking. However, further studies are needed to confirm such pattern between smoking and serum levels of PTH.

Although the observed inverse association has been significantly reported among women in general and older ones in particular, the mentioned relationship between exposure to tobacco smoke and VDD is not confined to a specific age group or particular gender. Kassi et al. carried out a research on the relationship between the prevalence of VDD and lifestyle parameters including smoking in healthy young and middle-aged men. They observed a strong correlation between $25(OH)D_3$ and smoking in participants ($P < 0.001$). By the help of a multinomial logistic regression model, they showed that the probability of having vitamin D_3 inadequacy has increased in smokers up to 58% and 63% for 20–29 year and 40–50-year age subgroups, respectively, compared with non-smokers (Kassi et al., 2015). Maternal exposure to tobacco smoke during pregnancy can affect VD level and subsequently calcium metabolism in mothers and infants (Banihosseini et al., 2013; Díaz-Gómez et al., 2007; Khuri-Bulos et al., 2014; Lawlor et al., 2013). Diaz-Gomez and colleagues evaluated the effects of smoking on the vitamin D-PTH system during the perinatal period. In their cohort study with 61 mothers and newborns, declined serum levels of PTH in both mothers and neonates, as well as a significantly lower levels of 25(OH)D in neonates were observed (Díaz-Gómez et al., 2007). These findings have been also seen in another prospective cohort study where 7.6% of mothers reported a history of smoking in the gestational period and 72.4% of all mothers reported passive exposure to tobacco smoke during pregnancy. Their results showed that the prevalence of severe VDD in newborns was associated with maternal smoke exposure (Khuri-Bulos et al., 2014). In addition, those mothers who have smoked during their pregnancy had lower 25(OH)D levels across all their trimesters compared with non-smokers (Lawlor et al., 2013). In a most recent study, Chinellato and colleagues studies the association between S-25(OH)D level and parental smoking in 152 children who were suffering from asthma. Children with both nonsmoking parents benefited from a significantly higher serum level of 25(OH)D than those with both smoking parents (median of 20.5 ng/ml vs median of 14.5 ng/ml; $P < 0.001$) (Chinellato et al., 2018).

In addition to the depression of serum levels of VD metabolites, it has been shown that exposure to tobacco smoke can influence the intake of VD as well. A population-based survey of 2319 women conducted by Morabia et al. in Switzerland showed that tobacco smoke could cause the low intake of VD through changing the dietary taste (Morabia et al., 2000). Furthermore, VD malabsorption might be a possible hypothesis that needs experimental investigations to be testified. It is worth noting that after a long time (5 years) smoking cessation, similar intake of VD and calcium has been reported in both former and never smokers (Morabia et al., 2000). On the other hand, the impact of smoking quitting on maintaining or even increasing serum VD levels described in some studies confirms the crucial importance of tobacco smoke exposure in dysregulating VDES (Gilman et al., 2006; Jiang et al., 2016). Jiang and colleagues revealed that longer duration of smoking cessation (> 20 years) could result in higher VD levels in former smokers compared with current smokers (P for trend = 0.04) (Jiang et al., 2016). A related point to consider is the corrective action of smoking quitting in relation to the calcitriol-PTH axis. Indeed, undesirable changes imposed on vitamin D-PTH system by smoking could be reversible by smoking ceases (Need et al., 2002).

Accumulating evidence suggests the effect of smoking on the deterioration of different disorders interrelated to VD levels. It means exposure to tobacco smoke influences the state of a disease through the alteration of VD metabolism. Gestational diabetes risk (Dodds et al., 2016), activating Crohn's disease (Gilman et al., 2006; Jørgensen et al., 2013), high rates of depression (Ren et al., 2016), the risk of myocardial infarction (Deleskog et al., 2012), and increased markers of inflammation in HIV-infected individuals (Legeai et al., 2013) might be

Table 2
The effects of smoking on VDES.

Authors/country/study type	Participants/age	Exposure	Key results	Key conclusion
Chinellato et al. (2018)/ Italy/human	152 children/5–15 years old Boys: 84 Girls: 68	Passive smoking	Children with both nonsmoking parents presented significantly higher serum levels of 25(OH)D than children with both smoking parents.	Lower levels of VD were inversely associated with passive smoking exposure.
Jiang et al. (2016)/China/ cross-sectional	612 men/aged > 50 years	Smoking Current smokers: 188 Ex-smokers: 154 Never smokers: 270	1. Compared to never smokers, current smokers had lower serum concentrations of VD, and the concentrations decreased with the increasing number of cigarettes smoked per day. 2. Longer duration of quitting smoking was associated with higher VD level than current smoking (P for trend = 0.04).	Current smokers had lower VD than never smokers, and the association showed a dose–response pattern.
Dodds et al. (2016)/ Canada/nested case-control	395 gestational diabetes cases 1925 controls	Smoking Never or quit before pregnancy: 1456 controls and 279 cases Smoker in pregnancy: 354 controls and 87 cases	1. Smokers during pregnancy had 25(OH)D concentrations < 30 nmol/l and had an OR = 3.73 [95% CI 1.95, 7.14] compared to non-smokers with 25(OH)D concentrations ≥ 50 nmol/l. 2. An additive interaction was detected between smoking status and 25(OH)D.	The study supports the inverse association of VD status with gestational diabetes risk, particularly among women who smoke during pregnancy.
Kassi et al. (2015)/Greece/ human	181 men/20–50 years old	Smoking Smokers: 64 Non-smokers: 171	1. A strong correlation was found between 25(OH)D and smoking (P < 0.001). 2. 25(OH)D level was lower by approximately 4.3 ng/dl (P < 0.001) in smokers compared to non-smokers 3. A young smoker (20–29 years) had 58% increased likelihood of having VD deficiency compared to a non-smoker of the same age group (P = 0.041).	Smoking is a significant determinant of S-25(OH)D, while it increases significantly the likelihood of having VD deficiency.
Manavi et al. (2015)/USA/ human	22,196 adults/aged > 18 years	Cotinine Three smoking categories: non-smokers, passive smokers, and active smokers.	Female active-smokers had the lowest mean VD concentration and higher prevalence of VD deficiency and inadequacy within the overall population.	The cotinine blood serum concentrations can also affect VD concentrations.
Ren et al. (2016)/China/ human	194 patients with acute ischemic stroke/ 18–80 years	Smoking Smokers: 116 Non-smokers: 78	VD levels were significantly lower in smokers than in nonsmokers.	Higher rates of depression in smokers with acute ischemic stroke might be associated with lower VD levels induced by smoking.
Mulligan et al. (2014)/USA/ human	Control subjects and patients with chronic rhinosinusitis (CRS)	Cigarette smoke (CS)	1. CS exposure was associated with decreased circulating and sinonasal tissue 25(OH)D_3 levels in control subjects and patients. 2. CS exposure decreased expression of CYP27B1. 3. Epithelial cell conversion of 25(OH)D_3 to 1,25$(OH)_2D_3$ was reduced in patients with chronic sinusitis with nasal polyps (CRSwNP) and in the presence of CS.	Exposure to CS was associated with reduced 25(OH)D_3 levels and an impaired ability of human sinonasal epithelial cell (HSNEC) to convert 25(OH)D_3 to 1,25$(OH)_2D_3$.
Shinkov et al. (2015)/ Bulgaria/human	Men: 915 (45–49) Women: 1037 (51–55)	Smoking Male smokers: 273 Female smokers: 299	Male smokers had lower 25(OH)D than nonsmokers (40.2 ± 16.6 vs 43.6 ± 15.7 nmol/l, P = 0.004).	Smoking in the males was a risk factor for VD deficiency among Bulgarian urban population.
Banihosseini et al. (2013)/ Iran/cohort	108 pregnant women and their newborns	Smoking Passive smoking exposure: 54 Controls with no exposure: 54	1. The mean level of 25(OH)D in maternal serum was 9.28 ± 5.19 ng/ml in exposed and 5.26 ± 10.75 ng/ml in non-exposed group (P > 0.05). 2. The mean concentration of 25(OH)D in cord serum was 10.83 ± 6.68 ng/ml in the exposed and 11.05 ± 4.99 ng/ml in the non-exposed group (P > 0.05).	The serum VD level was not significantly different in mothers and infants between two groups, but it was lower in the exposed group.
Jørgensen et al. (2013)/ Denmark/cross-sectional	182 Crohn's disease patients (105 women and 77 men) 62 healthy controls (32 women and 30 men)	Smoking	Crohn's disease patients who smoked had lower VD levels (51 nmol/l) than patients who did not smoke (76 nmol/l), P < 0.01.	Patients who smoked had lower 25(OH)D levels than patients who did not smoke, independent of disease activity.
Legeai et al. (2013)/France/ cohort	355 HIV-infected persons	Smoking Smokers: 118 Non-smokers: 236	In multivariate analysis, smoking was independently associated with 25(OH)D < 10 ng/ml.	In this population, low 25(OH)D was associated with smoking.

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Table 2 (*continued*)

Authors/country/study type	Participants/age	Exposure	Key results	Key conclusion
Cutillas-Marco et al. (2012)/Spain/cross-sectional	132 women and 45 men/18 to 84 years old	Smoking Smokers: 19 men + 52 women Non-smokers: 25 men + 80 women	1. An increased risk of VD insufficiency among smokers was detected (odds ratio, 1.8; 95% confidence interval, 1.00–3.35). 2. Smoking was correlated negatively with levels of iPTH ($r = -0.24$; $P < 0.001$).	Smoking was associated with an increased risk of hypovitaminosis D (odds ratio, 1.8; 95% confidence interval, 1.00–3.35)
Deleskog et al. (2012)/ Sweden/cross-sectional	387 survivors of a first myocardial infarction/ < 60 years of age 387 sex- and age-matched controls	Smoking	1. Current smoking was significantly and independently associated with 25(OH)D in controls. 2. In both patients and controls, a significant inverse correlation was observed in univariable linear regression analyses between 25(OH)D and current smoking.	–
Soldin et al. (2011)/USA/ human	293 women/18–45 years	Smoking Active smokers = 107 Passive smokers = 86 Non-smokers = 100	A significant decrease in serum $25(OH)D_3$ concentrations was demonstrated in smokers and in passive smokers. A decrease in $25(OH)D_3$ with increasing smoke exposure was indicated.	There were significant differences in concentrations of certain steroid hormones between non-smokers, passive smokers, and active smokers, most notably for $25(OH)D_3$.
Hansdottir et al. (2010)/ USA/human	Primary lung epithelial cells	1. Cigarette smoke (CS) extract 2. Acrolein	1. CS and acrolein significantly reduced the generation of $1,25(OH)_2D$ by airway epithelium. 2. The effects of CSE and acrolein were reversed by aldehyde dehydrogenase. 3. CS extract decreased 1α-hydroxylase mRNA.	Cigarette smoke decreased the conversion of inactive to active form of VD in the lung cells.
Wasserman and Rubin (2010)/USA/cohort	62 men with HIV-1–seropositive patients/ median age 48 years	Smoking Current smokers: 11	Tobacco use was correlated with severe VD deficiency, $P = 0.03$.	Tobacco use might be associated with lower VD levels and severe deficiency.
Matsunawa et al. (2009)/ Japan/human	Human monocyte/macrophage-derived leukemia THP-1 cells and human breast carcinoma MCF-7 cells	Benzo[*a*]pyrene Cells were cultured with or without 30 nM $1,25(OH)_2D_3$ and/or 1 μM BaP for 48 h.	1. BaP enhances the expression of CYP24A1. 2. BaP stimulates $1,25(OH)_2D_3$ metabolism through CYP24A1. 3. BaP enhanced the hydroxylation of $1,25(OH)_2D_3$ by CYP24A1 in THP-1 cells.	1. BaP treatment enhances the inactivation of $1,25(OH)_2D_3$by increasing the expression of the VDR target gene CYP24A1. 2. Aryl hydrocarbon receptor (AhR) activation by BaP stimulates vitamin D_3 catabolism.
Díaz-Gómez et al. (2007)/ Spain/cohort	61 women and their newborns	Smoking Smoking group (n = 32) Non-smoking group (n = 29)	1. In smoker mothers, their newborns showed decreased serum PTH. 2. Newborns of smoker mothers also had significantly lower S-25(OH)D.	Smoking during pregnancy negatively influenced calcium-regulating hormones, which resulted in relative hypoparathyroidism in both mothers and their newborns.
Lorentzon et al. (2006)/ Sweden/cohort	1068 men/18.0–20.1 years old	Smoking Smokers: 93 Non-smokers: 975	Smokers had significantly lower S-25(OH)D levels than nonsmokers.	–
Supervia et al. (2006)/ Spain/cross-sectional	31 men, 43 women/mean age 32.2 (7) years	Smoking Smokers: 22 Never smokers: 52 Those who stopped smoking for one month: 15	1. Male smokers compared with never smokers showed lower body mass density (BMD) and lower serum iPTH levels. 2. In women, 25(OH)D levels were lower in smokers compared to never smokers (16.8 ng/ml vs 31.9 ng/ml $P = 0.002$).	Tobacco increased bone resorption and affected bone mass by some alterations in sex hormone metabolism, but also importantly by alterations on the vitamin D-PTH axis.
Jorde et al. (2005)/ Norway/human	205 people/aged > 29 years	Smoking Smokers: 54 Non-smokers: 151	1. The serum PTH levels were significantly lower in smokers than in non-smokers. 2. One year after quitting smoking, serum PTH levels were similar to those who had never smoked. 3. The smokers had a significantly lower intake of VD, lower serum levels of 25(OH)D and lower Ca absorption.	1. Intake of VD and S-25(OH)D was significantly lower in smokers. 2. Smoking negatively affected vitamin D-PTH axis.
Need et al. (2002)/ Australia/cross-sectional	405 postmenopausal woman/35–88 years old	Smoking Current smokers: 74 Ex-smokers: 79 Never smokers: 252	1. Serum calcitriol was lower in current smokers than non-smokers ($P < 0.001$). 2. Serum PTH was lower ($P < 0.001$) in current smokers than non- smokers.	1. Serum calcitriol was significantly correlated with intestinal Ca absorption. 2. Serum calcitriol was decreased in smokers proportionally to their decreased serum PTH. 3. Smoking-associated changes in the PTH-calcitriol axis was reversible when smoking ceases.

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Table 2 (*continued*)

Authors/country/study type	Participants/age	Exposure	Key results	Key conclusion
Iwaniec et al. (2002)/USA/ animal	140 female Sprague Dawley rats/eight months old	Nicotine for 3 months Group I: low-dose nicotine (6.0 mg/kg/ day) Group II: high-dose nicotine (9.0 mg/kg/ day) Group III: saline	Administration of nicotine at high doses resulted in lower serum 25(OH)D levels.	Nicotine may contribute to the decreased concentrations of 25(OH)D observed in smokers. Nicotine had a negative effect on 25(OH)D metabolism.
Szulc et al. (2002)/France/ cohort	719 men/51–85 years	Smoking Current smokers: 83 Ex-smokers: 405 Never smokers: 231	1. Current smokers had a lower 25(OH)D concentration than former smokers and never-smokers. 2. The average concentration of 25(OH)D was similar in former smokers and never smokers.	Low S-25(OH)D may explain, at least partly, the effect of tobacco on bone turnover.
Morabia et al. (2000)/ population-based study/Switzerland	2319 women/35–74 years old	Smoking Current smokers: 528 Ex-smokers: 560 Never smokers: 1231	1. Daily intake of calcium was lowest in heavy smokers (798 mg) and highest in never smokers (945 mg; $P < 0.0001$). 2. After 5 years of smoking cessation, former smokers had similar intake of calcium and VD to never smokers.	Female current smokers had lower dietary intakes of calcium and VD than never smokers.
Hermann et al. (2000)/ cross-sectional/ Denmark	2015 women/45–58 years	Smoking Current smokers: 832 Ex-smokers: 285 Never smokers: 898	1. S-25(OH)D levels were significantly lower in current smokers compared with nonsmokers. 2. S-25(OH)D levels were correlated inversely with the number of smoked cigarettes per day.	Serum levels of 25(OH)D and osteocalcin were lower in smokers, which may affect the rate of bone loss.
Brot et al. (1999)/Denmark/ cross-sectional	510 women/45–58 years old	Smoking Smokers: 254 Never smokers: 256	Compared to never smokers, smokers had significantly reduced levels of S-25(OH)D ($P = 0.02$), $1,25(OH)_2D$ ($P = 0.001$), and PTH ($P < 0.001$).	1. A significant effect of smoking was found on the metabolism of calcium and VD 2. Smoking seems to depress the serum levels of 25(OH) D, $1,25(OH)_2D$, and PTH.
Fung et al. (1999)/USA/ animal	Adult female rats/7 months old	Nicotine/three months saline (n = 9/group), low dose nicotine at 3.0 mg/kg/day (n = l0/group) or high dose nicotine at 4.5 mg/kg/day (n = 11/group)	Animals that were administered with nicotine had significantly lower levels of 25(OH)D than controls.	Nicotine administration may adversely affect bone formation and decrease body storage of VD.
Fung et al. (1998)/USA/ animal	Adult female rats/7 months old	Nicotine/two months Saline (n = 7/group), Nicotine (3.0 mg/kg/day) (n = 7/group) or nicotine (4.5 mg/kg/day) (n = 7/group)	Nicotine-treated rats showed a lower level of 25(OH)D compared with controls ($P < 0.01$).	Nicotine administration resulted in decreases of serum 25(OH)D by about 30%.

associated with lower VD levels triggered by smoking. Significant and independent association between smoking and 25(OH)D concentrations has been reported in current-smoking patients (Deleskog et al., 2012; Jørgensen et al., 2013; Legeai et al., 2013). Through a case-control study, Dodds et al. revealed an inverse correlation between VD status and gestational diabetes, especially among women who smoked during pregnancy (Dodds et al., 2016). This inverse association was also reported among two cohorts of HIV-infected individuals between tobacco use and severe VDD [25(OH)D < 10 ng/ml] (Legeai et al., 2013; Wasserman and Rubin, 2010). In two studies exploring the relationship between VD status and smoking in patients with acute ischemic stroke and myocardial infarction, VD concentrations were significantly lower in smokers compared with non-smokers.

3.5.1. Tobacco smoke can potentially target almost all points of VDES

Although the mechanisms through which smoking interrupts the VD metabolism is poorly defined and still remain unknown, on the ground of the foregoing evidence summarized in the Table 2, making some highly likely assumptions is presumably by the help of a chain of experimental-based deductive reasoning.

The sufficiency of serum VD level plays a decisive role in the bone health subsequent to calcium intake and serum parathyroid hormone levels. Under normal conditions, serum 25(OH)D and $1,25(OH)_2D$ levels are negatively correlated with the serum level of PTH (Cheng et al., 2003; Holick, 2006). Through a cross-sectional study with 944 healthy participants divided into three groups of age (30–45 years, 50–65 years, and 70–85 years), calcium intake (< 800 mg/d, 800–1200 mg/d, and < 1200 mg/d), and S-25(OH)D level (< 10 ng/ml, 10–18 ng/ml, and < 18 ng/ml), Steingrimsdottir et al. evaluated the importance of high levels of 25(OH)D and calcium intake in serum intact PTH (iPTH). After adjustment for relevant factors, such as smoking, it was observed that serum PTH was lowest in the group with a serum 25(OH)D level of > 18 ng/ml but highest in the group with an S-25(OH) D level of < 10 ng/ml. They revealed that at low S-25(OH)D level (< 10 ng/ml), the calcium intake of < 800 mg/d vs > 1200 mg/d was significantly associated with higher serum PTH ($P = 0.04$) (Steingrimsdottir et al., 2005). Therefore, they reasoned that VD adequacy is much more important than high calcium intake in maintaining the optimum level of serum PTH. Accordingly, in response to the decreased level of VD, an increase in PTH level is expected; however, under exposure to tobacco smoke serum levels of both 25(OH)D and PTH have been lowered markedly (Brot et al., 1999; Cutillas-Marco et al., 2012; Jorde et al., 2005; Need et al., 2002; Supervia et al., 2006). Hypoparathyroidism has been discovered in both mother and their newborns under maternal smoking (Díaz-Gómez et al., 2007). It has been speculated that the dropped level of PTH in individuals exposed to tobacco smoke may be as a result of a small unmeasurable change in serum ionized calcium, a reduction in secretion or a rise in degradation of the hormone (Brot et al., 1999; Need et al., 2002). Due to the presence of endocrine disrupters in tobacco smoke, it is expected to see smoking-derived deleterious impacts on the VDES similar to the case regarding the reduction of vitamin D-PTH axis. Notably, in comparison to nonsmokers, smokers suffer from a significant decline in BMD caused by the impairment of calcium absorption, which in turns is attributed to the imposed destructive changes on vitamin D-PTH system (Brot et al., 1999; Jorde et al., 2005; Need et al., 2002). The association between lower BMD and smoking along with the declined concentration of VD have been described in current and former smokers (Lorentzon et al., 2006; Szulc et al., 2002). In line with the abovementioned studies, recent observations have demonstrated that lower concentrations of steroid hormones, as well as 25(OH)D, are associated with passive and active cigarette smoking (Lorentzon et al., 2006; Shinkov et al., 2015; Soldin et al., 2011; Szulc et al., 2002). There is further evidence based on a cross-sectional study of 405 postmenopausal women where poor calcium absorption in smokers has been associated with declined level of PTH (which leads to decreased renal hydroxylation of the storage form of VD to active structure) (Need et al., 2002).

Acrolein is an environmentally ubiquitous volatile organic compound (VOC) (Amini et al., 2017). This unsaturated aldehyde is responsible for a considerable part of cellular and molecular adverse effects of tobacco smoke. Through an in vitro study, the effects of cigarette smoking extract (CSE) and acrolein on the conversion of $25(OH)D_3$ to $1,25(OH)_2D_3$ were separately studied by Hansdottir and colleagues. They found that both of them had the capability to significantly reduce the generation of active vitamin D_3 in the airway epithelial cells. It is of note that the effects of CSE and acrolein were reversed by the enzyme aldehyde dehydrogenase (Hansdottir et al., 2010). This enzyme catalyzes the oxidation of aldehydes by addition of oxygen rather than by removal of hydrogen—that is, it converts aldehydes to carboxylic acids (Marchitti et al., 2008). The reduction of 1α-hydroxylase under exposure to CSE was observed as well. Consequently, lower level of $1,25(OH)_2D_3$ could contribute to the overexpression of inflammatory factors in smokers (Hansdottir et al., 2010). In a similar investigation, Mulligan et al. genetically scrutinized the effect of cigarette smoke (CS) on the levels of vitamin D_3 and its conversion to bioactive form in patients with chronic rhinosinusitis. They found that CS could impair the capability of epithelial cells in the conversion of $25(OH)D_3$ to $1,25(OH)_2D_3$ by the downregulation of CYP27B1 expression. CS exposure also was associated with declined circulating level of $25(OH)D_3$ (Mulligan et al., 2014). In vivo and in vitro exposure to other components of tobacco smoke such as nicotine and Benzo[*a*]Pyrene (BaP) can decrease body storage of 25(OH)D and $1,25(OH)_2D$ (Fung et al., 1999; Fung et al., 1998; Iwaniec et al., 2002; Matsunawa et al., 2009). By using an array of research, Fung et al. demonstrated that long- and short-term treatment with nicotine, the principal and addictive alkaloid in tobacco, significantly decreased S-25(OH)D in female rats (Fung et al., 1999; Fung et al., 1998; Iwaniec et al., 2002). Interestingly, such negative correlation between VD serum concentrations (< 20 ng/ml) and serum cotinine, the main metabolite of nicotine, has been reported among American females with different ethnic backgrounds. Based on the results, female active-smokers have the lowest mean VD concentration and higher prevalence of VD deficiency and inadequacy within the overall population in the U.S. (Manavi et al., 2015). 24-Hydroxylase is a member of the cytochrome P450 superfamily of enzymes encoded by the CYP24A1 gene involved in the metabolism of VD. It catalyzes reactions including 24-hydroxylation of 25(OH)D and $1,25(OH)_2D_3$ resulting in VDD. SNP rs4809957, located in the 3′ untranslated region of CYP24A1 at 20q13.2, interacts with smoking dose (Dong et al., 2012). Moreover, BaP, a PAH found in tobacco smoke, increases the catabolism of $1,25(OH)_2D_3$ in human monocyte/macrophage-derived THP-1 cells by enhanced expression of CYP24A1. In other words, BaP enhances the production of 25-hydroxyvitamin D_3 24 hydroxylase (CYP24A1), which leads to inactive metabolites of $24,25(OH)_2D$ and $1,24,25(OH)_3D$, and consequently decreased serum level of VD (Fig. 4) (Matsunawa et al., 2009). Indeed, dysregulation of genes that encode those enzymes involved in VD metabolism would be one of the possible mechanisms engaged in tobacco smoke-originated VDD.

Skin plays the most important role in the provision and metabolism of VD. Smoking (Ernster et al., 1995) and solar ultraviolet radiation (Pillai et al., 2005) have been known as extrinsic factors inducing an aging effect on human skin. Facial wrinkling is a marker of skin aging. Lopez Hernandez et al. discovered strong evidence of accelerated skin aging among smokers. They found a statistically remarkable effect of smoking habit (OR = 3.1; 95% CI = 1.28–7.76; $P = 0.008$), sun exposure (OR = 1.50; 95% CI = 1.25–1.80; $P = 0.05$), and age (OR = 1.18; 95% CI = 1.13–1.23; $P = 0.024$) on facial wrinkling (López et al., 1995). Increasing skin aging can diminish the capability of skin in the conversion of 7-DHC to precholecalciferol substantially (Holick, 1995). Using a cross-sectional study of 299 never smokers, 551 former smokers and 286 current smokers, a positive association between pack-years smoking and facial wrinkle score has been revealed.

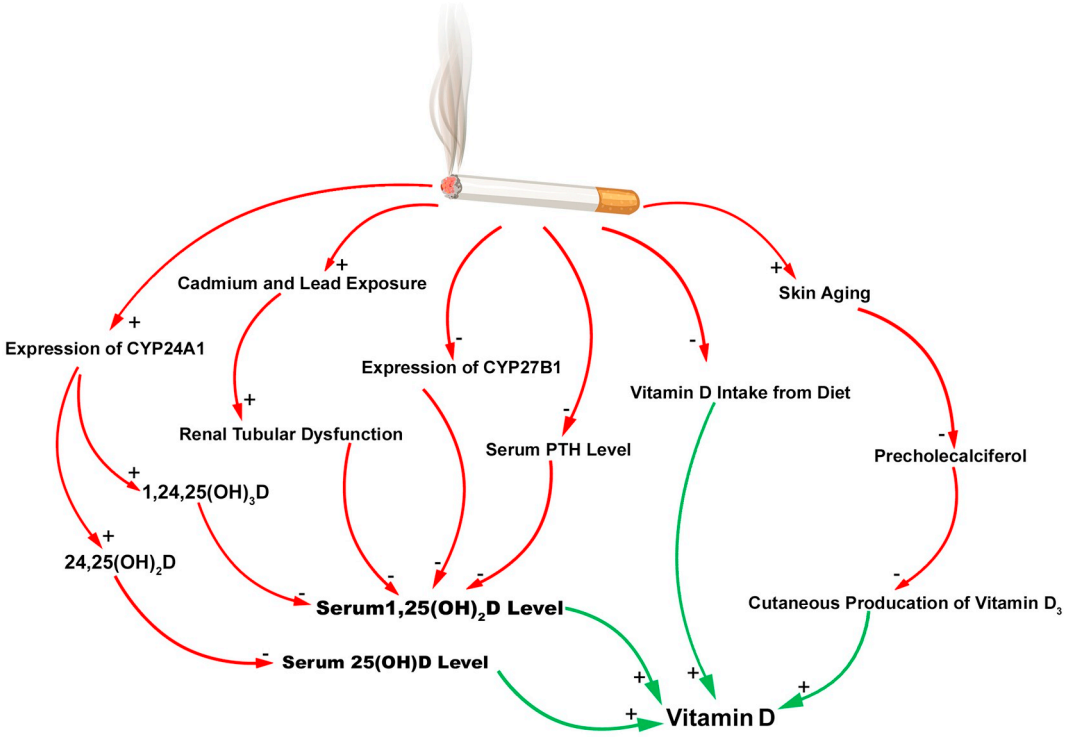

Fig. 4. Potential mechanisms related to the disruption of VDES by tobacco smoke. The positive and negative signs on the end of the arrows imply increasing and decreasing the targets, respectively. Red arrows originated from the cigarette result in decreasing serum 25(OH)D and $1,25(OH)_2D$ levels, VD intake from diet, and the cutaneous production of VD. These four items determine the VD level of individuals. From a systematic point of view, cigarette smoke leads to depression of VD levels in humans. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

The relative risk of moderate/severe wrinkling was estimated for current men smokers as 2.3 (95% confidence interval CI = 1.2, 4.2) compared to women never smokers 3.1 (95% CI = 1.6, 5.9) (Ernster et al., 1995). Mechanistically, the induction of matrix metalloproteinases (MMPs) mediates photo aging. Concerning tobacco smoke, there is adequate evidence putting an emphasis on the reinforcing role of smoking in skin aging through activation of MMPs (Holick, 1995; Lahmann et al., 2001). A significant increase of MMP-1 mRNA has been reported in the skin of smokers compared with non-smokers, whereas no difference has been seen for the tissue inhibitor of MMP-1 (Lahmann et al., 2001). It should be pointed out that smoker patients with chronic obstructive pulmonary disease (COPD) are at high risk of VDD because they are more susceptible to skin aging (Janssens et al., 2010). Overall, since smokers are more prone to skin aging, it is anticipated that smoking-derived skin aging causes VDD through the disturbance in the cutaneous production of vitamin D_3.

The declined level of serum $1,25(OH)_2D$ observed in smokers might also be as a result of cadmium accumulation in the kidneys (Brot et al., 1999; Kido et al., 1989). Since the tobacco plant has a considerable capability to concentrate heavy metals in general (Cd and Pb in particular), tobacco smoke is one of the common and rich sources of Cd and Pb exposure (Lugon-Moulin et al., 2006). Accordingly, inhibiting VD activation mediated by Cd and Pb poisoning can be one of the mechanisms involved in VDD. Impaired kidney function is the central core of this pathway. Indeed, there are elevated serum cadmium and lead levels in smokers, which results in the deterioration of renal tubular function and glomerular dysfunction (Cooper, 2006).

Putting experimental and epidemiological findings together, as shown in Fig. 4, skin aging, simultaneous decrease of VD and PTH, disturbance in the intake of dietary VD, renal tubular dysfunction, and dysregulation of CYPs genes related to the metabolism of VD are most possible pathways that interfere with VDES via exposure to tobacco smoke. In Fig. 4, we have integrated all mentioned mechanisms in order to provide a comprehensive view of a wide, and to some extent independent, mechanisms that might lead to VDD. Accordingly, there is an internationally emerging consensus among researchers corroborating the claim that smoking enhances the risk of VDD and severe VDD. Nonetheless, further investigation in the genetic analysis of suspected CYPs enzymes is needed to clearly ascertain metabolic mechanisms responsible for the reported smoking-derived VDD.

4. Summary and conclusion

This review integrated various pieces of evidence that exposure to air pollution, environmental chemicals, and smoking (with endocrine disrupting properties) can negatively interfere VDES and in most cases lead to VDD. To the best of our knowledge, the possible mechanisms that may be more likely disturbed and induce low serum levels of VD include: (1) decreased intestinal intake of VD, (2) decreased cutaneous production of cholecalciferol, (3) the modulation of genes involved in VD homeostasis, particularly CYPs, and (4) decreased local production of calcitriol in target tissues. Nevertheless, we still need mechanistic studies to explain precisely the biochemical pathways for mentioned chemicals. Therefore, we are in need of conducting more epidemiologic and experimental investigations on those sorts of environmental contaminants, which have the potency to cause VDD, so that involved mechanisms would be delineated more clearly.

Based on the presented evidence and potential mechanisms, monitoring serum level of VD in individuals with high exposure to the mentioned stimuli, and consuming higher amount of VD fortified foods and supplements by people settled in polluted areas are recommended in order to minimize the detrimental impacts on VDES. It is expected that the correction of VD status result into two vital achievements. First, it ameliorates anti-inflammatory and anti-oxidative capabilities in order to effectively deal with inflammatory-oxidative conditions originated from environmental toxicants. Second, such action averts the dramatic decrease of serum VD under conditions of exposure to environmental contaminants, and maintains related biochemical

pathways subsequent to keeping VDES well balanced. Accordingly, since pregnant women, on the one hand, are susceptible to VDD, and on the other hand, susceptible to environmental pollutants, recent investigations recommend a VD screening program and VD supplementation for those pregnant women who need it. These actions potentially could lead to a substantial decrease in related adverse pregnancy outcomes, especially in environmentally polluted areas (Holick, 2018; Rostami et al., 2018).

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Declarations of interest

None.

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