A review of aggravating factors of the occupational noise-induced health effects

Ebrahim Darvishi [1], Rostam Golmohamadi [2]

[1] Department of Occupational Health Engineering, Environmental Health Research Center, Research Institute for Health Development, Kurdistan University of Medical Sciences, Sanandaj, Iran. (corresponding author)

[2] Department of Occupational Hygiene, School of Public health and Research Centre for Health Sciences, Hamadan University of Medical Sciences, Hamadan, Iran.

Corresponding author's e-mail address: darvishi.hse@gmail.com

ABSTRACT

Noise-induced health effects are exacerbated by many other risk factors. This study aimed to systematically review the epidemiological literature of the aggravating risk factors of the health effects due to occupational noise exposure. PRISMA and MOOSE guidelines were followed. PubMed, Science Direct, and Google Scholar were searched up until 15 December 2019 in English, and Persian with appropriate keywords on combined effects of occupational noise, and co-exposure to noise and other factors. A total of we found 150 articles that were relevant and had sufficient quality for analysis. Overall, 15 risk factors were identified include at the four groups; chemical (solvents, heavy metals, and other chemicals), physical (lighting, heat, vibration, and cold), personal (age, gender, genetics, smoking, medication, contextual diseases) and occupational (workload, and shift work). Hearing loss, hypertension, reduced performance, and cardiovascular strains, are the most important the combined effects due to concurrent exposure to noise and other risk factors. Therefore, in the Hearing Conservation Programs, besides noise, aggravating factors of noise effects should also be taken into account.

Keywords: Noise Effects, Combined Effects, Combined Exposure, Occupational Exposure, Aggravating Factors

INTRODUCTION

Noise is a stressor that excessive exposure to high levels of it is very rampant in the occupational environment (Skogstad et al. 2016). Worldwide about 600 million workers are exposed to noise pollution in the workplaces according to a recent estimation from NIOSH (NIOSH 2012). Studies have shown that about 22 million US employees (about 7% of the total national population) are exposed to excessive noise in the workplace. In other industrialized countries 12 to 15 % of all workers are daily exposed to excessive noise. This ratio is equal to 4 to 5 million people in Germany (Basner et al. 2015). World health organization (WHO) estimated that about 278 million people suffer from mild to

severe hearing loss in the world which 16% of it is due to occupational noise exposures. Occupational noise exposure has caused the hearing loss in Europe and US 7 to 21% and 18% respectively. In Iran, according to the environment and labour health center, it can be estimated that more than 2 million workers are exposed to harmful noise in their workplace. Also, a review shows that the weighted average equivalent sound pressure level [L_{Aeq}] and average hearing loss during 15 years in Iranian workers was 90.29 dB(A) and 26.44 dBHL respectively (Soltanzadeh et al. 2014). These data together show that noise-related hearing problems may affect up to one-third of the world's population (Basner et al. 2015). Studies show that noise also has many non-auditory effects. Annoyance, disturbance in verbal communication, sleep disorder, cardiovascular diseases and hypertension, increased heart rate, association with type II diabetes, the effects of neurological and psychological disorders such as annoyance, irritability, impaired cognitive performance and the side effects such as reduced work performance and increased risk of accidents are all non-auditory effects of noise (Basner et al. 2014; Ismaila and Odusote 2014).
In the workplace, workers are simultaneously exposed to a considerable number of stressors including a variety of deleterious physical, chemical, and biological agents, ergonomic unfavorable conditions, allergens, safety risks, and psychological factors. Workers' exposure to the combination of harmful factors in the workplace is associated with health effects and safety consequences (Miyakita et al. 1990). In the workplace, evaluation of occupational combined exposure to several risk factors and their interaction effects is very complex because there are many confounding factors (Schwela et al. 2005). Effects due to of combined exposure are often intensifying, while exposure to an agent alone often has less effect (Chao et al. 2013). Thus, simultaneous exposure to several risk factors or stressors may be a synergistic, additive, potentiation, antagonism effects or without effect. Many observational, experimental, and review studies have shown that simultaneous exposure to occupational noise and other harmful agents may lead to combined effects on health (Basner et al. 2015; Lie et al. 2016). Hence, this paper reviews the literature on the combined effects of concurrent exposure to occupational noise and other factors.

Materials and Methods

By reviewing the scientific literature, a systematic and critical analysis, of the retrieved papers about the combined effects of occupational exposure to noise and intensifying factors, was performed. Scientific literature search included the following databases: Web of Science (1950), Scopus (1995), Medline (via PubMed) (1946), Science Direct (1985) and Google Scholar (1985) and as well as Cochrane Collaboration Summaries. Also, a search strategy was developed for each database. The search was conducted using following free-term keywords in the title, abstract, text format using controlled vocabulary (MeSH): combined effects of occupational noise", and "exacerbating factors of noise effects". The search was completed in November 2016.

Inclusion and exclusion criteria

The inclusion criteria were exposure to occupational noise in combination with different kinds of risk factors which exacerbate the noise-induced health effects and the statistical association between the combined exposure and health outcomes. In this review, we have mainly focused on studies of occupational, observational and experimental, restricted to original articles published in English and Persian journals. This included articles that focused on combined effects due to simultaneous exposure to noise and any other risk factors (i.e. co-exposure to noise and other physical or chemical agents). The studies related to environmental noise were excluded. All titles and abstracts from the literature search were assessed against the inclusion criteria. References that we judged to be potentially relevant were read in full text and assessed for inclusion. In order to assessment of studies' methodology and quality, the comprehensive checklist of the National Institute of Occupational Health was used. The checklist was developed based on the checklist of Ariens (Ariëns et al. 2000) and Hoogendoorn (Hoogendoorn et al. 1999) for observational studies. Therefore, study population, exposure level to noise (Equivalent Continuous Sound Level), data and confounding control of studies was evaluated. A total of, we identified 149 articles that met the inclusion criteria and were eligible for this review. These were cross-sectional studies (N = 93), longitudinal studies (N = 22), experimental (N=26) and others (N = 8). A flow chart showing the study selection is presented in Figure 1 (prisma).

Fig 1. Flow chart of the studies identification and selection process (prisma)

We identified 16 important risk factors (in four categories) in the workplace, which can intensify the noise-induced health effects in simultaneous exposure to noise and each of them. So, according to the literature review, we outlined four broad categories of risk factors that aggravate occupational noise effects: personal factors, occupational factors, physical agents, and chemical agents (Table 1). The results of the review were presented based on these four categories. Also, in the end, the levels of evidence and risk of combined effects of each were determined based on the design and quality of articles reviewed. The level of evidence was determined based on the number of citations, methodological quality and design, validity, and applicability of studies results (Low – Medium– High). Moreover, the level of combined risk is the degree of effect intensification caused by the simultaneous presence of two factors or agents that was determined based on design and study type, the methodological, validity of data, and the study population. These effects include Additive, Synergistic, Potentiation, and Antagonism effects[12]. An additive effect is the combined effect produced by the action of two or more agents, being equal to the sum of their separate effects. Wherein

combine of two or more risk factors produces a total effect that is the same as the arithmetic sum of the single effects (2 + 2=4). A synergistic effect is an effect arising between two or more agents or factors that is greater than the sum of their individual effects (2+ 2=25). The potentiation effect is an interaction between two factors (one with (2) and another without effect (0)) so that the no-effect agent enhances the total effect (0+2=10). In other words, the enhancement of one agent effect by another so that the combined effect is greater than the sum of each one alone. Antagonism effect is wherein two or more agents in combination have an overall effect that is less than the sum of their individual effects. It is opposite of synergistic (5+0=2)[12].

Table 1: Aggravating risk factors of noise-induced health effects

Category	**Aggravating Risk Factors**
personal factors	Age, Gender, Genetic background, Smoking, Medication, Contextual diseases
Chemical agents	Carbon monoxide, Heavy metals, Solvents, Chemical substances
Physical agents	Lighting, Heat, Vibration, Cold
Occupational factors	Workload, Shift work

1. Personal factors

1.1. Noise and age

Hearing loss is mainly related to increasing age[13]. The interaction between noise exposure and aging on noise-induced hearing loss (NIHL) is complicated, and it might be an additive effect. Age-related hearing loss (ARHL) increases with age, but the NIHL begins after about 3–5 years of excessive exposure to high levels of noise. NIHL does not increase to the same extent in older persons as in younger persons because older persons already have ARHL. In frequencies that have already suffered severe hearing loss, age has a limited effect on NIHL. With aging, the death of hair cells increases in the cochlear. Also, with aging, other parts of the hearing apparatus such as the auditory nerve and cognitive functions might be affected[14]. Rubak et al. (2006) reported that in employees exposed to noise for more than 20 years compared to employees that exposed less than 20 years, the risk of hearing loss was >20 dB higher[15]. In a cross-sectional study, Somma et al. (2008) compared the hearing of 184 male cement workers (daily noise exposure level >85 dB) with 98 workers non-exposed to noise (controls)[16].

They reported that a hearing loss of 5 dB in the young workers (age 21–30), and 20 dB among the old workers (age 51–60), compared to the controls. Moreover, in another cross-sectional study, Loukzadeh et al. (2011) showed that with increasing age and work experience, the mean hearing threshold in 4kHz and 8kHz frequency significantly increased in the 372 workers in a ceramic industry (mean age: 35±7.1 year) exposed to noise greater than 85 dB(A)[17]. In another cross-sectional study, Golmohammadi et al. (2013) studied the NIHL in 1062 of tractor manufacturing workers (mean age 43.2±6.9 year and the equivalent noise exposure (Leq) was > 85 dB(A)). The study showed that hearing loss increased by aging and the work experience. Besides, they reported that with the increase of one unit in Leq, experience, and age, the standardized regression coefficients (β) of hearing loss were 0.303, 0.327, and 0.12, respectively[18]. Also, in a prospective, population-based, longitudinal study of individuals aged 70-75 years (432 men and 581 women) from an epidemiological investigation, Hederstierna and Rosenhall[19] have reported an association between aging and NIHL. This study supports the additive model of NIHL and ARHL. Overall, the literature suggests the correlation of NIHL to increasing age as an additive model so that aging increases NIHL compared to noise exposure alone (additive model).

1.2 Noise exposure and gender

Although, there are few studies in term of the role of gender on the occupational noise effects. However, it is probably an effective factor[3]. In two cross-sectional study from Beaver Dam, Wisconsin, Cruickshanks et al. (1998) (N=3753)[20] and Nash et al. (2011) (N = 3285)[21] reported that hearing loss was associated with male gender, and occupational noise exposure. In a prospective study of 804,535 soldiers, Helfer (2011) reported that men lose hearing more than women in the same exposure to noise greater than 85dB(A)[22].

In the field of non-auditory effects, in a laboratory study on 169 students (80 females and 89 male), Beheshti et al. (2019) reported that noise-induced annoyance among females was more than men[23]. Röösli et al. (2014) examined sleep disturbances in 733 women and 533 men due to exposure to noise (Leq>40 dB(A)). They suggested that noise-induced sleep disturbance in men was greater than women (at the same level of noise exposure). This study suggests that men are more vulnerable[24]. Girard et al.

(2014) investigated cardiovascular disease among 8,910 retired workers exposed to occupational noise (>80 dB(A)/8 h). They reported that the effect of noise on the prevalence of cardiovascular diseases is a main risk factor in women (more than men)[25].

1.3 Noise and genetic background (genetic predisposition or heredity)

Genetic probably is a predisposing factor for noise-induced health effects, and there are several genetic studies of the relationship between genetics background and NIHL[26–30]. Gates et al. (1999) confirmed that genetic background is very important for hearing[31]. Konings et al. (2009) reported a correlation between exposure to noise and genetic variation in a survey of 1261 male noise-exposed workers (three occupational noise exposure categories, ≤85dB(A), 86–91dB(A) and ≥92dB(A)) and they suggested that PCDH15 and MYH14 may be NIHL susceptibility genes[32]. Also, Shen et al. (2012) suggested that GSTM1 polymorphism is associated with susceptibility to NIHL in a survey in 444 NIHL and 445 normal-hearing Chinese workers exposed to (three occupational noise exposure categories, 85 dB(A) or less, 86 to 91dB(A), and 92 dB(A))[33]. NIHL is a sensorineural, rampant, and complex disease that can even result from the interaction of exposure to noise and genetic background [34]. Hence, heredity also plays an important role in it [35]. There are numerous studies on humans and animals showing that phenotypic variability may affect hearing. In another experimental study, Yousaf et al. (2016) reported a phenotypic variability has a great variety of reasons, including physical agents in workplace (such as noise exposure)[36]. In a chinese case-control study, Xu et al. (2016) studied ten single nucleotide polymorphisms in the genes POU4F3 and GRHL2 among 3790 workers who worked in a steel factory and exposed to occupational noise higher than 80 dB(A)[37]. They confirmed that genetic variations in POU4F3 and GRHL2 are predisposing factors of NIHL and associated with NIHL. Also, in a case–control study with 326 hearing loss cases and 326 controls of steelworkers, Yang et al. (2016) showed that EYA4 genetic variant and its interaction with noise (cumulative noise exposure ≥98 dB(A)) may contribute the susceptibility to develop NIHL[38]. Shen et al. (2016) examined genetic variation in APE1 gene among 613 NIHL workers and 613 normal-hearing workers (age range 21–59 years) were exposed to noise 85-92 dB(A). They found that the APE1-656

T>G polymorphism may modify the susceptibility of NIHL[39]. Overall, researchers from different countries found mutations of the many genes associated with hearing loss. In other words, genetic variations have an important role in NIHL.

Animal studies

Moreover, in an experimental study on a population of inbred mouse strains exposed to 10-kHz octave band noise at 108 dB sound pressure level in 5–6-wk, Lavinsky et al. (2016) have demonstrated that genetic architecture of NIHL provides strong evidence for gene-by-noise interactions in NIHL[40].

1.4 Noise and smoking

Smoking is potentially relevant to hearing loss[41,42] and all of the studies we identified, suggest that smoking is an exacerbating risk factor for NIHL[43–46]. Starck et al. (1999) found that combined exposure to noise and smoking contributed significantly to NIHL among 199 professional forest workers (exposed to LP=95dB(A)) and 171 shipyard workers (exposed to LP=86dB(A))[47]. In a cross-sectional study, Mehrparvar et al. (2015) evaluated the combined effects of noise exposure and smoking (at least 1 pack/year) on standard pure tone audiometry (PTA) and distortion product otoacoustic emissions (DP-OAEs) on 224 workers (105 smokers and 119 nonsmokers) exposed to noise (Leq= 91 dB(A)) in the tile and ceramic industry. They reported that mean DP-OAE response amplitude at frequencies higher than 1000 Hz is significantly higher in smokers compared to non-smokers[48]. Also, in two cross-sectional studies, contained 8543 subjects (3593 smokers and 4950 non-smokers) exposed to occupational noise (>85dB(A)), and of 622 male workers (252 smokers and 370 non-smokers) exposed to occupational noise (Leq=91dB(A)) Sung et al. (2013)[49] and Mohammadi et al. (2010)[50] showed that smoking accompanied by noise exposure have an interactive effect on hearing loss. Also, the hearing thresholds of workers exposed to noise were significantly influenced by smoking. Zamanian et al. (2013) in a cross-sectional study of 270 male workers of rubber factory (135 smokers and 135 non-smokers) revealed that hearing loss was significantly associated with co-exposure to noise ($L_{Aeq,8h}$ ≥85 dB(A)) and smoking and smoking is a booster factor for NIHL[51]. In another cross-sectional study, Tao et al. (2013) examined the effect of smoking on NIHL in 517 male workers (199

nonsmokers and 318 smokers) exposed to $L_{Aeq,8h}$ ≥90 dB(A) (The average noise exposure duration was 17.28 year). The study suggested that interaction between smoking and occupational noise exposure may be additive (hearing loss was 1.94 times more than noise alone)[52]. In a population-based cross-sectional study from 1723 women exposed to noise > 85 dB(A), Ferrite et al. (2013) were suggested a dose–response relationship of smoking for the noise effect on hearing loss[53].

In investigating the effect of smoking on hearing loss of 150 refractory's factory male workers (55 smokers and 95 non-smokers), who exposed to 89±2.63 dB(A), Mofateh et al. (2017) emphasized that smoking has an additive role in hearing loss of workers exposed with excessive noise[54].

Also, in the field of non-auditory effects, two studies were found. In a retrospective study, Alimohammadi and Danesh (2014) evaluated the combined effect of occupational noise exposure (Leq > 88.83 dB(A)) and smoking on hematological parameters of 50 workers (11 smokers and 39 none smokers) in a food manufacturing plant. The results of the study indicated that RBC and WBC parameters in smokers with noise exposure were higher than non-smokers at the same level of noise exposure[55].

Also, in a cross-sectional study, Rahimpour et al. (2016) investigated the effect of noise exposure (Leq > 85 dB(A)) and smoking on blood pressure of 604 steelworkers. Results demonstrated no significant differences in the hypertension of smokers exposed to noise[56].

Animal studies

Moreover, in an animal study, Hashemi et al (2019) investigated the combined effect of exposure to cigarette smoking and noise on hearing loss of three groups of male rats for 8 h and 10 days inside the exposure chamber. they observed the permanent change in rats' hearing exposed to both cigarette smoking and noise. A total of, it can be concluded that smoking significantly exacerbates NIHL and has an additive effect on NIHL[57].

Table 2. Summary of the results of the literature review of the combined effects of personal factors and noise

personal factors	The level of combined risk		Level of evidence	Effects	Comments	Study
	Quantitative	**Qualitative**				
Noise & Aging	Exposure to Leq > 85 dBA and mean of aging > 45 year, mean exposure years > 3-5	Additive	High	Hearing loss,	High age is strongly related to hearing loss	[13], [14], [15], [16], [17], [18], and [19].
Noise & Gender	Exposure to Leq > 80 dBA and Male gender	Potentiation	High	Hearing loss, sleep disturbance	Men lose hearing more than women and women are more vulnerable to non-auditory effects.	[20], [21], [22], [23], [24], and [25].
Noise & Genetic background	Exposure to Leq > 80 dBA and genes POU4F3	Potentiation	Medium	Hearing Loss	Genetic background predispose for NIHL (explains a great part of the individual variation in hearing loss)	[26], [27], [28], [29], [30], [31], [32], [33], [34], [35], [36], [37], [38], [39], and [40].
Noise & Smoking	Exposure to Leq > 85 dBA and smoking (a pack per month during 5 year)	Additive	High	Hearing Loss, Hypertension,	Smokers have NIHL higher than nonsmokers	[42], [43], [44], [45], [46], [47], [48], [49], [50], [51], [52], [53], [54], [55], and [56].

2. Chemical agents

2.1 Noise and carbon monoxide (CO)

Carbon monoxide is a toxic asphyxiant that impairs the oxygen exchange to tissues by producing carboxyhemoglobin (COHb)[74]. International commission on biological effects of noise (ICBEN) has reported that carbon monoxide exacerbates effects of exposure to occupational noise on hearing[75]. Studies show that CO can reduce oxygen levels in the cochlea (cochlear hypoxia) particularly in the basal region[76]. Noise exposure also induces cochlear hypoxia[77]. Thus, chronic cochlear hypoxia caused by concurrent exposure to noise and CO can lead to significant effects on hearing of workers in workplaces such as the steel industry[78]. Lacerda and Leroux (2005) compared the hearing thresholds of a group of workers exposed to noise (90dB(A)) and CO, with another group of workers exposed only to noise (90dB(A)). The results revealed that hearing thresholds (at high frequencies 3, 4, and 6 kHz) was significantly

higher in the noise + CO group compared to the noise group only[79]. In an observational study, Ferreira et al. (2012) investigated hearing effects induced by simultaneous exposure to the CO (ranged from 200 to 700 (ppm)) and noise (range of 86.7-93.5dB(A)) in 80 male workers in a steel plant. They concluded that hearing loss was %12 higher in the noise + CO workers compared to the noise workers alone[80].

Also, in terms of the non-auditory effects, we also identified one published study. In a retrospective and cross-sectional study, Zeigelboim et al. (2015) evaluated the neurological symptoms in 30 Brazilian fishermen. fishermen exposed to a combination of CO (100 ppm) and noise (97.3 dB(A)). The results revealed that neurological symptoms (fatigue, dizziness, anxiety, mental impairment, and depression) were significantly more in the workers exposed to a combination of noise and CO than those exposed to noise alone[81].

Animal studies

In an experimental study, Young et al. (1987) examined the combined effects of exposure to noise (LAeq = 90 dB(A)) and CO (1200 ppm) on hearing of 16 male Long-Evans hooded rats. They reported that CO potentiates high-frequency auditory threshold shifts induced by noise[78].

2.2. Noise and solvents

We identified 21 published studies describing the combined effects of occupational exposure to noise and Solvents. Solvent exposure is associated with hearing loss[82,83]. Morata et al. (1993) reported that the combination of noise (88-97 dB(A)) and solvents (370 ppm) increased the hearing loss compared with exposure to noise and solvents separately (a synergistic effect)[84]. Sliwinska-Kowalska et al. (2004) studied the combined effects of noise and solvents, such as styrene, xylene, n-hexane, and toluene on hearing loss of 1117 workers from different industries[85]. They reported that the combination of noise (Leq>85dB(A)) and solvents caused a hearing loss more than exposure to noise alone. Kim et al. (2005) examined toxic effect mixed solvents on the auditory system of 542 male workers in the aviation industry, who exposed to noise (levels ranged from 85 dB(A) to 101 dB(A))[86]. They suggested that the prevalence of hearing loss in the group exposed to noise and mixed solvents simultaneously (54.9%)

was higher than those in the other groups (6%). Jacobsen et al. (1993)[87] in a Danish cross-sectional study of 3282 men (exposed to both noise>86DB(A) and solvents), Botelho et al. (2009)[88] in study of 155 Brazilian steel workers (exposed to both toluene and noise=80-95dB(A)), Mohammadi et al. (2010)[89] in an cross-sectional study included 411 workers (exposed to both mixed solvents and range noise: 79 dB(A) to 86 dB(A)), Metwally et al. (2012)[90] in an retrospective case–control study of 223 workers in a painting production factory (exposed to both Leq=90dB(A) and toluene and ethanol, hexane, xylene, acetone, butanol), Unlu et al. (2014)[91] in an case-control study contained 469 truck plant workers (exposed to noise>85dB(A) and styrene (30 ppm)), and Chang et al. (2006)[92] in a case-control study contained 58 workers (exposed to both toluene and noise (Leq=78.6–87.1dB(A))) studied the effects of occupational exposure to noise and organic solvents on hearing loss. They have unanimously reported that combined exposure to mixed solvents and occupational noise can exacerbate hearing loss in workers. Also, in another cross-sectional study on 1029 workers of a tire manufacturing company, Pourzarea et al. (2016) have estimated that co-exposure to mixed solvents and noise (Leq>85dB(A)) can reduce the hearing of workers 1.74 times more than noise alone[93]. In a transversal retrospective cohort study, Lobato et al. (2014) on 198 workers in a metal graphics company, indicated that combined exposure to solvents (aromatic hydrocarbons, toluene, xylene, turpentine, oils, greases, lead chromates, and molybdate) and noise (Leq=85 to 93 dB(A)) can damage the peripheral auditory system[94]. Also, Sliwińska-Kowalska et al. (2003) compared hearing loss in 290 workers exposed to styrene (averaged concentration 61.8 ± 51.9 mg/m^3) and noise (range SPL=71.3–93 dB(A)) and 213 workers exposed to noise alone (range SPL= 70.3–97.4dB(A)) from a plastic boat factory. The study revealed that combined exposures to noise and styrene seem to be more ototoxic than exposure to noise alone and that the effects were at least additive, and perhaps synergistic[95]. In the study of 701 shipyard workers, the same authors reported that the combination of exposures to noise, and xylene and toluene were additive[85]. Also, in a study of 346 rayon wool workers (105 exposed to noise (80–90 dB(A) and 132 exposed to a combination of noise (80–90 dB(A) and carbon disulfide), Chang et al. (2003) reported that the hearing loss was higher in exposed groups compared to the non-exposed[96].

In terms of non-auditory effects, the combined effects of occupational exposure to noise and solvents on blood pressure also were studied. In a cross-sectional study, Attarchi et al. (2013) in the study of 471 workers of a car manufacturing company, demonstrated that co-exposure to noise (SPL>85 dB(A)) and mixed organic solvents (benzene, toluene, xylene, and acetone) has an additive effect in the prevalence of hypertension[97].

Animal studies

Styrene is a cochleotoxic chemical. In an experimental study on Adult male Brown-Norway (n = 114) rats weighing over 300 g, Campo et al. (2014) discovered that a co-exposure to impulse noise (85 dB SPL) and styrene (300-ppm, 6 h per day, 5 days per week, for four weeks) is more damaging on the organ of Corti than exposure to continuous noise alone or co-exposure to continuous noise and styrene[98]. In an experimental study, Fetoni et al. (2016) found that styrene enhances the noise-induced oxidative stress in the cochlea and affects differently mechanosensory and supporting cells[99].

2.3. Noise and heavy metals

We identified 21 published studies on this topic. Lead, mercury, cadmium, and arsenic are suspicious of exacerbating the noise effects[100]. Lead has been introduced as a conclusive ototoxic[75]. Wu et al. (2000) examined the hearing loss in 220 employees that exposure to high levels of lead (56.9 ug/dL) and noise (Leq was 86 dB(A)) simultaneously, in a lead battery manufacturing plant[101]. They showed that the hearing threshold increased at 4 kHz with combined exposure. Also, in the study of 412 Taiwanese steelworkers, Hwang et al. (2009) reported an association between lead in blood and hearing loss[102]. Moreover, Farahat et al (1997)[103], Bleecker et al. (2003)[104], and also Forst et al (1997)[105] have confirmed a significant correlation between current blood lead levels and hearing thresholds in the workers exposed to noise. Mercury and mercury compounds (methyl mercury chloride, mercuric sulfide) often have been reported as ototoxic[106]. Several studies have been conducted regarding the effects of mercury exposure on the auditory system. Studies of Discalzi et al. (1993)[107], and Shlomo et al. (2002)[108] have shown that industrial exposure to inorganic mercury and

noise can cause auditory impairments. Cadmium also can cause hearing loss, and the synergistic effect of cadmium fumes on NIHL has been found[109]. Ozcaglar et al. (2001) examined the effect of exposure to noise (SPL=87dB(A)) and cadmium (2mg/kg) fumes and showed that hearing loss at 4 kHz and 6 kHz was more severely affected with combined exposure[110].

In the field of non-auditory effects, several studies have explored risk of hypertension due to occupational exposure to lead (Pb) and noise simultaneously. In a cross-sectional study, Rapisarda et al. (2015)[111] examined the relationship between occupational exposure to lead (Pb = 0.05 mg/m^3) and noise (occupational noise exposure >80 dB(A)) and risk of hypertension in 105 workers of a battery recycling plant. They concluded that occupational exposure to lead and noise associated with increased systolic and diastolic blood pressure (with an odds ratio of 1.2).

Animal studies

The combined effect of manganese has also been examined in an experimental study on hearing loss of rats exposed to noise (SPL=90 dB for 8 h/d) and manganese (moderate levels=10 mg $MnCl_2$/liter water) for 90 days. The results indicated that manganese in the presence of noise had a minor effect on auditory system[112]. Also, Kesici (2016) has reported that arsenic can cause hearing loss at frequencies of 125, 250, and 8000 Hz[113].

Table 3. Summary of the results of the literature review of the combined effects of chemical agents and noise

Chemical Agents	The Level of Combined Risk		Level of Evidence	Effects	Comments	Study
	Quantitative	**Qualitative**				
Noise & CO	Exposure to Leq>80dBA and CO concentration >200 ppm	Additive	High	Hearing loss, Fatigue , impaired cognitive performance	The CO induces cochlear hypoxia, in result, aggravate NIHL	[74], [75], [76], [77], [78], [79], [80], and [81].
Noise & solvents	Exposure to Leq > 80dBA and concentrations equal to 50-300 ppm	Synergistic	High	Hearing Loss, Hypertension	Styrene, toluene, hexane, xylene, acetone, butanol, trichloroethylene, and ethanol have combined effects to noise.	[84], [85], [86], [87], [88], [89], [90], [91], [92], [93], [94], [95], [96]. [97], [98], and [99].

Noise & heavy metals	Exposure to Leq = 80-95dBA and lead (Pb = 0.05 mg/m3), (manganese=10 mg MnCl2/liter water), cadmium (2mg/kg)	Synergistic	High	Hearing Loss	Lead, Mercury, Arsenic, Cadmium are combined effects.	[100], [101], [102], [103], [104], [105], [106], [107], [108], [109], [110], [111], [112], and [113].

3. Physical factors

3.1. Noise and lighting (illuminance)

A few studies are showing the combined effects of unfavorable lighting and noise. The most important of the combined effect of noise and unfavorable lighting in workplaces is impaired cognitive function[117] and visual[118]. All of the research literature was based on experimental work. In an experimental study of 12 desk workers (that subjects conducted three tests of 'letter cancellation 'hand precision,' 'two-hand coordination,' and 'tweezers dexterity'), Bhattacharya et al. (1989)reported the interaction effects of noise (70 and 100 dB) and illumination (50, 150, and 300 1x) on the speed and efficiency of the performance[119]. In another experimental study, the same authors confirmed increased performance error by combinations of illumination (500 lux) and quiet (60 dB(A)) and noise (100 dB(A)) on neuropsychological performance capability of 20 male college student[120]. In another experimental study, Gorai et al. (2007) found that illumination levels (250-350-550 lux) have a combined effect with noise (Leq>85dB(A)) on the operator's performance and with the increase of both the noise and illumination levels, the performance level decreases[121]. Mangipudy (2010) also suggested that the combined effect of extraneous sound and light seems to be a potential source of extrinsic cognitive load on students' achievement[122]. Moreover, in another experimental study, Liebl et al. (2012) found an interaction effect between acoustic (Leq=40 dB and the level of background noise =35 dB) and lighting (lighting of four fluorescent lamps with 60-50 lux) on cognitive performance and well-being in 32 healthy young subjects[123]. In another study, Amiri et al. (2015) examined the effects of combined exposure to noise and lighting on cognitive performance of 128 healthy young subjects[124]. They suggested that combined exposure to noise (SPL=95dB(A)), and unfavorable lighting (20 Lux) have adverse effects on parameters of cognitive performance (working memory, attention, and concentration). The study of the combined effects of more than two physical factors on humans is very complex. In an

analytical-descriptive study, Golbabaei et al. (2014) examined the combined effects of noise (79-85dB(A)), unfavorable lighting (25-42 Lux) and heat stress (WBGT=22-28ºC) on job performance using manual and mental tests in 30 employees of the auto parts manufacturer[125]. Their results indicated that simultaneous exposure with noise and high thermal stress index and low lighting increases the duration of manual and mental tests and reduced accuracy compared to each agent alone. Also, they pointed out that background noise can impair short-term memory. Cross-modal effects of noise (45, 55, 65, and 75 dB(A), and noise type Music, Water, Babble, and Fan), and illuminance (150, 500, and 1000 lx) were investigated in 60 university students (30 men and 30 women) in an indoor environmental chamber. The findings revealed that the acoustic conditions affected visual relaxation. The illuminance conditions did not affect acoustic perception. Cross-modal interactions were asymmetric between sound and illuminance in indoor environmental settings. Women were more sensitive to the perception of both acoustic and illuminance stimuli than men at a high level of stimulation[126]. In another empirical study**,** Liu et al. (2017) investigated the effects of noise type, and intensity (45, 65, and 85 dB(A)), and illumination intensity (600, 1000, and 200 lx) on reading performance[127]. They reported that illumination intensity too high (or too low) along with high noise level, impair reading performance more compared to noisy and normal illumination intensity conditions.

3.2. Noise and heat

Heat stress is also an environmental factor that can exacerbate noise-induced health effects[128]. In a cross-sectional study, Singh et al. (2010) confirmed combined effects of noise (Leq more than 90dB) and heat stress (WBGT higher than standard ACGIH/NIOSH equal to 36°C) on hearing loss in 350 male workers of the casting industry[129]. Also, in an experimental study, Chen et al. (2007) examined the combined exposure to noise (75, 85, and 95dB(A)) and temperature (22, 27, and 32ºC) on auditory fatigue of 14 healthy young subjects in a climatic chamber[130]. They concluded that heat stress (27, and 32ºC) enhance noise-induced temporary threshold shift.

In the field of non-auditory effects, also several studies have investigated the combined effects of noise and heat stress. Most of the research literature is based on experimental work. In an experimental study, Witterseh et al. (2004) confirmed the

interaction effect of temperatures (22-26-30ºC) and noise (55dB(A)) on increased subjective distress and fatigue in 16 male employees an open-plan office[131]. In another experimental study, Pellerin and Candas (2003) examined the combined effects of noise (35-85dB(A)) and temperature (14-34ºC) on the discomfort of 108 lightly clothed subjects (54 male and 54 female) [128]. They suggested that noise may alter thermal pleasantness in warm conditions. Moreover, in an experimental study, Tiller et al. (2010) examined the combined effects of noise (SPL was 39-55dB(A)) and heat stress (WBGT was 22-26°C) on comfort and performance of 30 healthy young subjects (16 females, 14 males). They found that thermal comfort was strongly affected by noise[132].

In a cross-sectional study in an iron foundry, Sen et al. (2014) reported that co-exposure to noise (85-90dB(A)) and heat stress (WBGT in the furnace unit was 33.73°C) increase the health risk of workers and consequently reduce the efficiency and the production[133]. Moreover, the study of the combined effect of noise and heat stress on the metabolic syndrome of 590 steelworkers, demonstrated that the prevalence of metabolic syndrome in workers exposed to noise and the high temperature was 1.12 times more than workers exposed to noise alone[134].

A study has also been done on hypertension. In an experimental study, Dehghan et al. (2017) examined the combined effect of noise (75-95dB(A)) and heat stress (40°C) on hypertension of 14 healthy young subjects in a climatic chamber[135]. They reported that the heat intensified noise-induced hypertension, and the blood pressure in concomitant exposure was significantly higher compared to noise alone. Fouladi Dehghi et al. (2019) reported that the interactive effect of noise (>85 dB(A)) and heat (WBGT>32 °C) significantly decreases the VO2 max value (maximal aerobic capacity) in 50 students compared to noisy and the lower WBJT conditions[136].

3.3. Noise and vibration

Vibration can affect physical and mental performance in the job[137,138]. Sleep disorders[139], difficulty in concentration[138], fatigue[138], depression[137], irritability[140], shock[140], loss of grip strength, blanching (white finger), and anxiety are health effects that were reported due to vibration. Numerous studies have reported the combined effects of noise and vibration, and for many years vibration and vibration-induced effects, with combined exposure to noise, have been considered as possible risk factors

for developing hearing loss[7,138,139,141,142]. We identified 11 published studies describing the combined effects of occupational exposure to noise and vibration. In an experimental study of healthy young subjects, Zhu et al. (1997) reported that combined exposure to noise (LAeq >90 dB(A)) and hand-arm vibration (HAV) (30 m/s2, 60 Hz) gave a greater temporary hearing loss than exposure to noise only[143]. In a cohort study of hearing loss in 15757 mining and forestry male workers who suffered from white finger and had combined exposure to noise (Leq equal to 80-90 dB(A)(8h)) and whole-body vibration (WBV), Turcot et al. (2015) reported that in workers with vibration-induced white fingers (VWF), hearing loss at low and high frequencies was higher compared to workers without VWF[144]. Also, in a longitudinal study, Iki et al. (1989) reported that hearing loss in the 2–4-kHz range was more in individuals with VWF than controls grope[142]. Pyykkö et al. (2007) studied the shipyard workers, forestry workers, metal workers, and patients referred to a clinic. They reported that workers with Raynaud disease (due to vibration) were more susceptible to hearing loss at 4 kHz than others[145]. In a cohort study, Pettersson (2013) examined the risk of NIHL in 276 workers of the heavy engineering industry, that exposure to noise (Laeq 88 dB with a range of 75 to 99 dB A) and machines induced hand-arm vibration (HAV) (7.6 to 11 m/s2)[14]. They found that HAV increases the risk of NIHL at 0.5 kHz, 1 kHz, 2 kHz, and 4 kHz frequencies. Also, in an experimental study, Sisto et al. (2016) investigated the combined effect of exposure to noise (SPL=94dB(A)) and HAV (0.5 m/s^2), on the distortion product otoacoustic emission (DPOAE) level in 12 volunteers[146]. They found a synergistic adverse effect of co-exposure to noise and HAV on the cochlear function. Generally, studies have confirmed synergistic effects of HAV and noise on the cochlear function.

Moreover, in the field of non-auditory effects, in an experimental study, Huang and Griffin (2014) presented a regression model to predict the discomfort caused by simultaneous exposure to noise (sound pressure levels ranging from 64 to 82 dB(A)) and whole-body vibration (WBV = 0.079 to 1.262 m/s^2) in 24 healthy young subjects (12 males and 12 female)[147]. They concluded that discomfort caused by a combination of noise and vibration is more than each alone. Besides, the noise had a masking effect of the judgment on the discomfort caused by vibration. In summary, in all experimental studies, the psychological effects include increased stress, annoyance, and discomfort,

decreased performance and decreased ratings of alertness, and disruption in the horizontal tracking tasks has been reported due to combined exposure to noise (>78dB(A)) and whole-body vibration (1.1 m/s^2)[137]. Note that more effects of combined exposure to noise and vibration have been reported in low levels of noise[138]. Also, in a cross-sectional study, Dzhambov and Dimitrova (2016) studied the synergistic effects of co-exposure to noise (80-90dB(A)) and whole-body vibration and the risk of heart diseases in 3149 workers of Bulgaria[148]. Most of the studies suggest that whole-body vibration is a risk factor for getting heart diseases from noise exposure.

Table 4. Summary of the results of the literature review of the combined effects of physical agents and noise

Physical Agents	The Level of Combined Risk		Level of Evidence	Effects	Comments	Study
	Quantitative	Qualitative				
Noise & Lighting	Illuminance<100 lux and exposure to Leq >55dBA	Potentiation	Low	Disturbance and cognitive impairments	Undesirable lighting quality and low illuminance exacerbate non-auditory effect due to noise	[117], [118], [119], [120], [121], [122], [123], [124], [125], [126], and [127].
Noise & Heat	exposure to Leq >65 dBA and wet bulb global temperature >24ºC	Additive	Medium	Hypertension, Metabolic syndrome	Heat aggravate noise-induced hypertension and exacerbate cognitive performance	[128], [129], [130], [131], [132], [133], [134], [135], and [136].
Noise & Vibration	exposure to Leq >80 dBA and acceleration of V>5 m/s^2 (auditory effects) - exposure to Leq >65 dBA and acceleration of V>0.5 m/s^2 (non-auditory effects)	Synergistic	High	Hearing Loss, Fatigue, Annoyance, Decreased performance	Vibration exacerbate all noise effects.	[7], [14], [138], [139], [140], [141], [142], [143], [144], [145], [146], [147], and [148].

4. Occupational factors

4.1. Noise and workload

Mental workload defined as the expenses imposed on the operator to achieve a certain level of performance[151]. High mental and physical workload causes fatigue, decreased performance, memory loss, impaired cognitive function, and irritability[152]. Also, the low mental workload can lead to depression and decline in cognitive performance [153]. The studies show that exposure to occupational noise can increase the mental workload[154,155]. On the other hand, high mental workload exacerbates noise-induced

health effects[156]. There were only five published studies of exposure to a combination of occupational noise and high workload. In an experimental study of 14 healthy young subjects, Chen et al. (2007) investigated the combined effects of noise (75, 85, and 95dB(A)) and workload (% VO2max= 10, 30, and 60) on noise-induced hearing temporary threshold shift (NITTS)[130]. The results of study showed that workload enhance NITTS.

Also, in terms of non-auditory effects, in a follow-up study comprised 1502 middle-aged men employed in industries, Koskinen et al. (2011) reported that occupational exposures to noise (mean noise level >80 dB) and physical workload concurrently entail increased levels of blood pressure (>140/90 mm Hg) compared to noise (>130/89 mm Hg) or workload alone (>130/80 mm Hg) alone and risk of coronary heart disease (RR was 2.19 times greater than each alone)[157]. Moreover, in another cohort study (N=1288 for heart disease follow-up, N=884 for SBP follow-up) of male workers, Virkkunen et al. (2006) found that combined exposure to noise and increased workload levels entails a significant increase in systolic blood pressure (SBP) than exposure to noise alone[158]. In an experimental study on 14 healthy young subjects, Dehghan et al. (2013) reported that exposure to noise (at SPL>85 dB(A)) and high workload (50 min heavy work) in thermal comfort condition increase the heart rate[159]. In another experimental study on work memory of 31 healthy subjects, Golmohammadi et al. (2019) reported that noise-induced impaired cognitive function increases at higher task difficulty (subjective workload) levels[160]. Overall, the number of studies for this is still limited, however, the evidence suggests that workload intensifies noise-induced health effects.

4.2. Noise and shift work

Shift work is probably a risk factor for noise-induced health effects. Because many health effects include fatigue, insomnia, gastrointestinal problems, cardiovascular disease, and decreased cognitive performance have been proven in association with night work[161]. Therefore, it can be expected that night work aggravates the noise-induced health effects.

In a cross-sectional study, Chou et al. (2009) compared the hearing loss of 218 male workers (146 workers had an 8-hour work schedule, and 72 workers had a 12-hour work schedule) at a semiconductor factory that exposed to noise levels exceeding

85dB(A)[162]. They reported that the hearing loss in shift workers with a 12-hour work schedule was significantly lower compared to shift workers with an 8-hour work schedule. The number of studies on this topic is limited, but it appears that shift workers lose hearing more than non-shift workers.

Also, in terms of non-auditory effects, we identified several studies on this topic. In the study of 254 workers in a chemical plant (including 188 shift workers and 66-day workers that both exposed to noise (Leq, 8hr was >85 dB), Saremi et al. (2008) reported that mean level of noise-induced fatigue in shift workers was more compared to day workers[163]. Also, they suggested that the combined effect of shift work and concurrent exposure to noise on fatigue is synergistic. In a follow-up study of 1804 middle-aged male workers with exposures ranging from 80 to 100 dB(A) and shift work in occupational category, Virkkunen et al. (2006) concluded that shift work and exposure to continuous noise entailed an excess risk for coronary heart disease[158]. Also, in a cross-sectional study, Attarchi et al. (2012) investigated the combined effects of noise (SPL>85dB(A)) and shift work on blood pressure levels of 331 workers in a rubber manufacturing company[164]. Their study showed an additive effect on systolic and diastolic blood pressure due to simultaneous exposure to noise and shift work.

Table 5 shows a summary of the results of the literature review about the combined effects of occupational factors and noise and also the level of risk and evidence.

Table 5. Summary of the results of the literature review of the combined effects of occupational factors and noise

Occupational factors	The Level of Combined Risk		Level of Evidence	Effects	Comments	Study
	Quantitative	Qualitative				
Noise & Workload	exposure to Leq > 75 dBA, and score of workload>50/100	Additive	Low	Hearing Loss, Fatigue, Disturbance	Workload may aggravate health complaints due to noise.	[130], [155], [156], [157], [158], [159], and [160].
Noise & Shiftwork	exposure to Leq > 80 dBA, and 8h night work during >5 year	Both Additive, and Synergistic	Medium	Cardiovascular Effects, Hypertension, Fatigue	Shiftwork is strongly related to cardiovascular diseases and hearing loss and aggravate this effects in concurrent to noise	[158], [162], [163], and [164].

Discussion

This review focused on the combined effects of occupational exposure to noise and other risk factors that aggravate the noise effects using a systematic assessment of the quality of eligible studies. Many of the included studies were cross-sectional because the majority of the occupational studies for good enough description of occupations is cross-sectional. We believe that these studies provide valid data because the outcome data come from objective sources and are usually field measurements of noise and other risk factors. Most of the studies we identified have investigated only combined effects of risk factors on hearing, and the evidence for non-auditory effects is still limited. Thus, the main weakness of the studies is that mainly auditory effects have studied. Further studies are needed in the field of non-auditory effects due to concurrent exposure to noise and other risk factors. Another limitation is that in some studies, the degree of combined effects has not clearly expressed and only has been cited the existence of a combined effect. Overall, we concluded the level of combined risk each of the factors based on design and study type, the methodological, validity of data, and the study population. Moreover, in the study of combined effects in occupational environments, there are many confounding factors. Therefore, the study of combined exposure to stressors or multiple risk factors and trying to identify the effects of their interactions on human health is very complicated.

According to the literature review and the level of evidence, 16 risk factors can exacerbate the noise-induced health effects. The combined effects of occupational exposure to noise and each risk factor of aging, smoking (personal factors), vibration, heat (physical agents), chemicals, solvents, shift work, CO, and metals (chemical agents) have been well known. Because, there is stronger evidence about their combined effects with noise as aggravated risk factors of noise-induced health effects, and the statements made well accepted. Confounding factors and also exposure population have well been considered, in the concurrent exposures noise to these factors. Moreover, these factors are more important than others. Because in most workplaces, noise and these factors co-exist. Besides, their risk level on noise-induced health effects is more.

Hearing loss is mainly related to increasing age. Men lose hearing more than women do. Heredity also plays a part. Smoking seems to be a certain intensifying for NIHL.

Moreover, the combined effects of solvents, CO, metals, and chemicals with noise are mostly on hearing. Overall, toluene, styrene, and trichloroethylene seem to lead to hearing damage. Nonetheless, the research findings on other solvents such as xylene, n-hexane, and ethylbenzene are more uncertain. Lead, mercury, arsenic, and cadmium intensify noise-induced central and peripheral hearing loss compared to the noise alone. Reviews of experimental studies suggest that concurrent WBV may enhances both noise-induced hearing and non-hearing effects. Heat intensifies most of the noise-induced non-hearing effects, but the research findings on hearing effects are more uncertain. It appears that shift work may enhance noise-induced sleep disorder and also harmful effects of noise on the cardiovascular system.

However, the evidence of the combined effects of occupational exposure to noise and each risk factor of gender, genetic, medication, lighting, cold, and workload were weaker and are needed further studies. Besides, it is necessary to consider the effect of confounding factors. Diabetes, hypertension, and cholesterol seem to have also affect NIHL, but the evidence for noise-induced non-hearing effects is still limited.

Noise is a non-specific biological stressor which can affect the body's entire[1]. According to the results of the literature review and the general adaptation syndrome [165], the concurrent exposure to single or multiple stressors (an event that threatens an organism's well-being) leads to a three-stage bodily response. Therefore, upon perceiving a stressor (such as noise), the sympathetic nervous system is stimulated, and the body's resources mobilize to meet the danger. The result of this reaction is a "fight-or-flight" response named "Stress". Stress is the organism's total response (reaction of neurologic and endocrinologic systems) to environmental demands or pressures. The body makes an effort to limit stress. If stressor persists, the body focuses on resources and resists against the stress and remains on alert. The result of this resistant is a response named "Strain". The strain is deformation, disturbance, or deflection of physiological in the body due to the persistence of stress. In other words, the strain is an unstable physiological response to get rid of the stressor. Hence, the parasympathetic nervous system is stimulated and attempts to return many physiological functions to normal levels. The strain is directly proportional to the stress and is a load applied to a proportional limit. Upon the stressor is removed, stress is back to normal, and the strain also becomes zero. These actions have taken to avoid the

noise is called coping. But, if the exposure to stressor or stressors continues beyond the body's capacity, the resources become exhausted, the body strained beyond the proportional limit and is susceptible to effect and disease.

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