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The primary aim of *World Journal of Meta-Analysis* (*WJMA*, *World J Meta-Anal*) is to provide scholars and readers from various fields of clinical medicine with a platform to publish high-quality meta-analysis and systematic review articles and communicate their research findings online.

WJMA mainly publishes articles reporting research results and findings obtained through meta-analysis and systematic review in a wide range of areas, including medicine, pharmacy, preventive medicine, stomatology, nursing, medical imaging, and laboratory medicine.

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MINIREVIEWS

Diabetes mellitus: An overview of the types, prevalence, comorbidity, complication, genetics, economic implication, and treatment

Adekunle Sanyaolu, Aleksandra Marinkovic, Stephanie Prakash, Martina Williams, Yashika Dixon, Chuku Okorie, Verner N Orish, Ricardo Izurieta

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Abstract

Diabetes is one of the deadliest diseases. Due to its effects on the lives of people, it has attracted a lot of attention recently. The causes of the various forms of diabetes, including type 1 and type 2, were discussed along with how they affect those who have the disease. Younger people are more prone to type 1 diabetes than older people, who are more likely to develop type 2. The treatment options and strategies for the two forms of diabetes were also discussed in addition to how the disease affects the quality of life of people. Among several factors that were explained, it has been shown that people from low and middle-income countries are more prone to having diabetes. Additionally, the condition is more likely to affect some races more than others. It is associated with obesity. According to statistics, those who are poor are more severely affected by the disease. The progression of the disease over time has been associated with an increase in disability and mortality.

Key Words: Diabetes mellitus; Type 1 diabetes; Type 2 diabetes; Diabetes; Insulin; Blood glucose

Core Tip: Diabetes is a disease that has significant financial consequences in the patients and can also be lethal. There are two types: type 1 and type 2 diabetes. The former is more prevalent among children, whereas the latter is more prevalent among adults. Diabetes is known to cause severe complications, resulting in misery and premature death. Fortunately, interventions and treatment options are available.

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INTRODUCTION

Diabetes is a chronic condition characterized by abnormalities in insulin secretion or action, or sometimes both[1]. Insulin is a hormone released by the pancreas that works as the primary messenger for moving glucose from consumed meals to flow from the bloodstream into the body's cells where it is used for energy[2]. Diabetes affects the entire system and causes issues in specific organs such as the eyes, nerves, and kidneys[3]. It affects 9.0% of the adult population globally, according to the World Health Organization[2,4,5]. It is a developing pandemic that may be traced back to the fast rise in obesity and inactivity[3], being classified into two types: Type 1 (insulin-dependent) and type 2 (non-insulin-dependent) (adult-onset)[1]. Diabetes causes serious health problems globally, primarily increasing the risk of heart disease and other complications[4]. It affects 80.0% of the population in low and middle-income nations, and in wealthy countries, adults between the ages of 35 and 64 years are most affected[4].

Furthermore, the most economically and socially marginalized persons have the heaviest burden of living with the condition and are most financially impacted[4,5]. Its consequences are assessed not only by the rise in the prevalence presented every year per capita, but also through the rising number of complications and deaths[4]. While the prevalence of most infectious illness continues to diminish as technology improves and life expectancy increases, the impacts of diabetes continue to increase[4]. This article reviews diabetes mellitus with an overview of the types, prevalence, comorbidity, complication, genetics, economic implication, and treatment.

METHODOLOGY

The electronic databases PubMed, Google Scholar, and Med Line Plus were searched for the review of literature. The search was limited to peer-reviewed publications between January 1994 and November 2022 for the compiled data. Publications that had keywords including "diabetes mellitus" were chosen. The articles were then included after being evaluated for relevance to the topic (Figure 1).

DIFFERENT TYPES OF DIABETES

Diabetes is a metabolic illness in which insulin plays a central role. There are several pathogenic pathways at work in the etiology of this illness[1]. They vary from autoimmune death of pancreatic beta cells, resulting in chronic insulin insufficiency, to a disease inhibiting insulin action[1]. The cause of this condition is an aberrant carbohydrate, lipid, and protein metabolism caused by insufficient or even defective insulin activity[1]. The major cause of hyperglycemia is a deficiency in either secretion or effect of insulin at one or more sites along its route of action[1].

TYPE 1 DIABETES MELLITUS

Type 1 diabetes mellitus (T1DM) is triggered by an autoimmune response in which the body targets

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Figure 1 Article selection.

insulin-producing cells[1]. The level of beta cell breakdown in T1DM varies among patients, being fast in some and exceedingly sluggish in others[1]. Keto-acidosis is the most common initial symptom of the illness in most people[1]. Others exhibit symptoms such as fasting hyperglycemia as well as keto-acidosis in the context of environmental variables[1]. Although some people may preserve adequate beta-cell activity to prevent keto-acidosis, many individuals eventually become insulin dependent and develop keto-acidosis[1]. As the condition advances, insulin production decreases, and C-peptide levels become low, and often may become undetectable[1]. A variety of reasons, including heredity, environmental factors, and idiopathic causes have been linked to the autoimmune degradation of beta cells[1]. Some cases of T1DM have an unclear origin as seen in some people of African or Asian descent[1].

TYPE 2 DIABETES

Type 2 diabetes mellitus (T2DM) affects 90.0%-95.0% of the diabetic population. T2DM is characterized by a complicated process in which the fundamental issue is a balance between insulin production by beta cells and insulin action, resulting in insulin resistance to insulin-stimulated glucose in the blood[3]. Impaired glucose tolerance is the illness' intermediate stage that determines the risk of heart disease[1]. Many individuals with T2DM are obese, indicating that obesity may induce some sort of insulin resistance[1]. Keto-acidosis occurs spontaneously and gradually in this type of diabetes, and it is frequently triggered by the same conditions that cause T1DM such as stress and illness. Because of the absence of apparent symptoms, T2DM is commonly undiagnosed[3]. Most of the symptoms develop slowly and are frequently not severe enough to be detected[1].

REGIONAL OVERVIEWS

The diversity of socioeconomic and geographical parameters, prevalence, associated death, and health expenditure may all be used to assess the Global Perspective[1,2,5]. Most diabetics reside in less developed and economically disadvantaged parts of the world[5]. Eighty percent of the population is from low- to middle-income nations[1,2,5]. Different forms of diabetes are prevalent across the world, yet each has a distinctive impact on different populations[5,6]. Infectious diseases, such as human immunodeficiency virus and malaria, as well as poverty are prevalent in Africa[5]. A shift in lifestyle in urban and rural regions, has resulted to an increase in obesity. "Diabetes has taken precedence in this region" and others[5,6]. Europe is grouped into 56 countries, with socioeconomic levels ranging from low to high[7]. Age is the most important risk factor for diabetics. Diabetes is expected to affect 56 million people in Europe, with adults accounting for 8.5%[7]. The top three nations in the Middle East and North Africa with the highest comparative frequency are Saudi Arabia, Kuwait, and Qatar[6,7]. The rapid rise in economic growth, along with an aging population, has led to a substantial rise in the prevalence of T2DM[4]. Rapid urbanization, lower infant mortality, and increasing life expectancy are the primary drivers of the increase in T2DM prevalence[4]. North America and the Caribbean have the second-highest comparative prevalence of adult diabetes (9.6%)[4]. If the main North American countries of the United States (US), Mexico, and Canada were included in the figure because of their large population, the Caribbean islands would still have the greatest occurrence[4,7]. Diabetes affects 38.6 million individuals in this region, with the number anticipated to climb to over 50 million by 2035 [7]. The US had the highest number of diabetics, at 24.4 million[4].

DIABETES IN CHILDREN AND ADOLESCENTS

Diabetes is one of the most common disorders affecting school-aged children[8]. In 2012, around 208000 young persons under the age of 20 years in the US developed diabetes[8]. Additionally, during the COVID-19 pandemic, children with newly diagnosed T1DM had higher glucose and HbA1c levels, necessitating specific actions to increase clinician and public awareness[9]. T1DM had a global incidence rate of 19.73 per 100000 children in 2019 and 32.39 per 100000 in 2020[9]. The number of pediatric cases of new-onset T1DM, diabetic ketoacidosis, and severe diabetic ketoacidosis increased by 9.5% (T1DM), 25.0% (DKA), and 19.5% (severe DKA), respectively, during the first year of the COVID-19 pandemic compared to pre-pandemic levels[9].

A high proportion of children and adolescents with type 2 diabetes are also susceptible to insulin resistance and have a family history of T2DM[8,10]. Certain racial and ethnic groups, including African Americans, American Indians, Hispanic/Latino Americans, and some Asian and Pacific Islander Americans, have higher rates of T2DM[10]. Some children and adolescents with T2DM may not exhibit any signs or symptoms at all[10]. Other individuals' symptoms may resemble those of T1DM[10]. A toddler or teenager may feel tired, thirsty, or sick and urinate more frequently[10]. Weight loss, hazy vision, recurring infections, and delayed wound/sore healing are all possible symptoms[10]. Because symptoms vary so much, healthcare practitioners must identify and evaluate children and adolescents who are at high risk for the condition[10]. The key to controlling T2DM in children is a balanced diet and quantity management, as well as increased physical activity[10,11]. Metformin should also be recommended when T2DM is diagnosed[11]. However, data indicate that 50.0% of young people with T2DM will be unable to keep their hemoglobin A1c (HbA1c) below 8.0% on metformin alone, with or without lifestyle changes[11]. If metformin alone is insufficient to normalize blood glucose levels, insulin may be required[11,12]. At the time of diagnosis, blood pressure, lipid profile, microalbuminuria evaluation, and dilated eye examination are suggested[12].

DIABETES IN ADULTS

In 2021, diabetes was the eighth leading cause of mortality in the US, affecting more than 100000 people [13]. Nearly one-fourth of all US persons with diabetes are undiagnosed, according to the Centers for Disease Control and Prevention (CDC) National Diabetes Statistics Report[14]. Table 1 shows that this is particularly evident in younger adults aged 18-44 years[14]. More than 1/3 of the population with diabetes in this age range are unaware of or did not report having diabetes[14].

Though the trend in the incidence of diabetes among adults has been decreasing significantly since 2008, Table 2 shows that there were still 1.4 million new cases in 2019[15]. It is also worth noting that incidence rates are significantly higher among those with a high school education or less[16]. This indicates that more effort should be made on health education among those with lower scholastic achievements[15,16].

TREATMENT OF DIABETES AMONG PEOPLE AGED 18 YEARS OR OLDER WITH DIAGNOSED DIABETES IN THE UNITED STATES, 2015-2016

Diabetes management begins with healthy eating habits and physical activity. Since this may be challenging, medications are available to augment the achievement of better treatment results[17]. A retrospective, cross-sectional analysis of the 2003-2016 National Health and Nutrition Examination Survey data was carried out to investigate trends in the use of diabetes medications[17]. The study sampled 6323 patients[17]. Furthermore, those 18 years and older with an HbA1c greater than 6.4%, or a fasting plasma glucose greater than 125 mg/dL were included [17]. The percentage of patients taking any medication increased from 58.0% in 2003-2004 to 67.0% in 2015-2016[17]. The use of metformin and insulin analogs increased following American Diabetes Association recommendations in 2007 when metformin was and continues to be the preferred first-line therapy for T2DM[17]. Among patients on one therapeutic agent, the use of metformin increased from 33.0% in 2003-2004 to 74.0% in 2015-2016 [17]. Risk factors for T2DM in adults include: Overweight or obesity, age of 45 years or older, a family history of diabetes, decreased physical inactivity, and history of gestational diabetes[18]. Figure 2 shows the distribution of diabetes across races/ethnicity. Diabetes is most prevalent among American Indians and Alaska Natives (14.5%), followed by Blacks (12.1%), people of Hispanic origin (11.8%), Asians (9.5%), and Whites (7.4%)[19].

Table 1 Diagnosed and undiagnosed diabetes among people aged 18 years or older in the United States, 2019

Characteristics		Undiagnosed diabetics (number in millions)	Total diabetics (number in millions)
Total	28.5	8.5	37.1
Age (year)			
18-44	3.5	2.1	5.6
45-64	11.8	3.8	15.5
≥ 65	13.2	2.6	15.9
Sex			
Men	15.4	3.6	19.1
Women	13.1	4.9	18.0

Data sources: 2017–March 2020 National Health and Nutrition Examination Survey; 2019 United States Census Bureau data[14].

Table 2 New cases of diagnosed diabetes among people aged 18 years or older in the United States, 2018-2019

Characteristics	Population estimates, number in thousands	Incidence estimates, rate per 1000
Total	1398	5.9
Age in year		
18-44	401	3.2
45-64	703	10.1
≥ 65	293	5.8
Sex		
Men	723	6.6
Women	675	5.2

Data sources: 2018–2019 National Health Interview Survey and 2019 United States Census Bureau data[14].

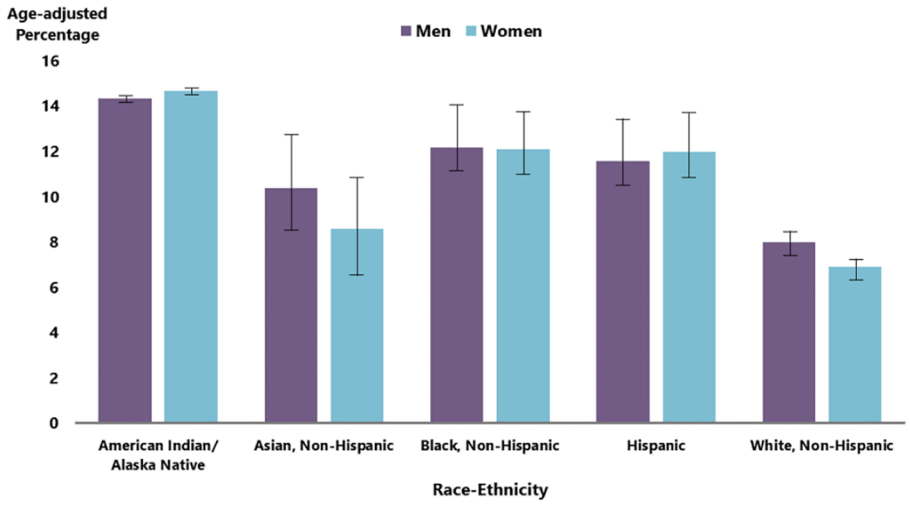

Figure 2 Diabetes by race/ethnicity. The age-adjusted estimated prevalence of diagnosed diabetes by race/ethnicity group and sex for adults aged 18 years or older in the United States, 2018–2019. Data sources: 2018–2019 National Health Interview Survey; 2019 Indian Health Service National Data Warehouse (for American Indian/Alaska Native group only)[19].

CO-MORBID CONDITIONS

The autoimmune diseases such as autoimmune thyroiditis (AIT), celiac disease (CD), Addison's disease,

and vitiligo are frequently linked to T1DM[19]. In comparison to 0.5% of the general population, CD prevalence in T1DM patients ranges from 1.5% to 10.0%[20]. It is important to note that people who develop both illnesses have an earlier age onset for TIDM than patients who just have T1DM[20]. Furthermore, 3.4% - 50.0% of people with T1DM also have AIT[20]. Anti-thyroid antibodies are developed in 11.0% - 16.9% of T1DM patients within the first year of diagnosis, with females being more frequently impacted[20]. Up to 2.0% of T1DM patients may have anti-adrenal autoantibodies[20]. It is commonly known that autoimmune diseases like diabetes and vitiligo are related. About 6.0% of diabetic children have vitiligo[20]. Additionally, T1DM has been linked to non-autoimmune diseases such as eating disorders[20].

The most common conditions seen in T2DM, according to previous research and American Diabetes Association guidelines, are hyperlipidemia, hypertension, obesity, depression, chronic obstructive pulmonary disease/asthma, coronary artery disease (CAD), chronic kidney disease (CKD), arthritis, cancers, neuropathy, heart failure, fractures, peripheral arterial disease, and retinopathy[21]. According to a study by Lin *et al*[21], persons over 65 years of age are more likely than those under 65 years to have multiple co-morbid conditions. Additionally, they discovered that older persons were less likely to be obese and depressed but more likely to have hyperlipidemia, hypertension, CAD, CKD, arthritis, malignancy, and heart failure[21]. With this information in mind, customized management plans should be created for frequent comorbidity clusters.

COMPLICATIONS

Diabetes can cause long-term harm to the heart, blood vessels, eyes, kidneys, and nerves. Smoking cigarettes, being overweight or obese, doing little or no physical activity, having high blood pressure, and hyperlipidemia are risk factors for developing diabetes complications[22]. According to a multi-national study, heart disease and stroke account for 50.0% of diabetes-related deaths[23]. In comparison to adults without diabetes, patients with diabetes over the age of 18 years have 1.7 times higher risk of dying from cardiovascular disease[24]. In 2011, the CDC found that nearly one-third of diabetics aged 35 years or older had a history of heart disease or stroke. It has been reported that coronary heart disease (21.9%) affects more people than stroke (9.1%)[22].

Diabetes has major complications that may be fatal, such as hyperglycemic crises, which include diabetic ketoacidosis and hyperglycemic hyperosmolar condition[20]. Death rates have progressively decreased over time, but 17.3 per 100000 people still die each year[24]. In 2011, 44.0% of all new cases of renal failure were caused by diabetes. In the same year, 228924 people of all ages were undergoing diabetes-related dialysis or a kidney transplant, while 49677 people of all ages started therapy for kidney failure[24]. The minor blood vessels in the retina are harmed by diabetic retinopathy, which causes blindness. Diabetes is responsible for 1.0% of blindness worldwide[23]. Furthermore, diabetes may result in amputations. Foot neuropathy raises the risk of developing foot ulcers, getting infected, and ultimately leading to an amputation[23]. Around 73000 non-traumatic lower limb amputations occurred in 2010 for adult diabetics. Overall, these patients comprise about 60.0% of all non-traumatic lower-limb amputations in adults over the age of 20 years[24].

GENETIC ROLE IN DIABETES MELLITUS: TYPE 1 DIABETES MELLITUS

One of the factors associated with the risk of T1DM is genetic variation. Some families have an inherited propensity for T1DM development[25]. It has been shown that the immune system can distinguish between proteins produced by the body's own cells and those produced by foreign invaders with the aid of the human leukocyte antigen (HLA) complex[25]. An increased risk of T1DM exists with some HLA variations on chromosome 6[25]. Hundreds of genes that are known to play a role in the immune system are found in the genetic sequence area. The genes frequently linked to T1DM have been identified to be part of the HLA class II genes. These genes include *HLA-DQA1, HLA-DQB1,* and *HLA-DRB1*[25].

An estimated 40.0%–50.0% of the heritable risk for T1DM is attributed to HLA class II genes[26]. Researchers discovered a significant link between T1DM and the haplotypes DQA1*0501-DQB1*0201 and DQA1*0301-DQB1*0302 in Caucasian populations[26]. A haplotype is a group of single nucleotide polymorphisms that are located on the same chromosome[26]. Further research revealed that different races have different high-risk haplotypes for T1DM, such as DRB1*07-DQA1*0301-DQB1*0201 for African Americans, DRB1*09-DQA1*0301-DQB1*0303 for Japanese people, and DRB1*04-DQA1*0401-DQB1*0302 for Chinese people[26]. Additionally, it was discovered that DRB1*15-DQA1*0602-DQB1*0102 were protective and linked to a lower incidence of T1DM in most populations[26]. Recent studies reveal that independent of HLA class II genes, other genes in the central, class I, and extended class I areas may also enhance the risk of T1DM[26].

People with high-risk DRB1-DQA1-DQB1 haplotypes are substantially more likely to develop T1DM than people without such a haplotype[25]. It is reported that there is an approximately 6.0% absolute risk for Caucasian people with two susceptibility haplotypes to develop T1DM by the time they are 35 years old. However, in populations where T1DM is uncommon, this number is much lower (1.0% among Asians). Two other genes, insulin (INS) and cytotoxic T lymphocyte-associated 4 (CTLA-4), are also known to affect the risk of T1DM as shown in Table 3[27,28].

GENETIC ROLE IN DIABETES MELLITUS: TYPE 2 DIABETES MELLITUS

The metabolic illness T2DM is characterized by hyperglycemia and a lack of insulin in the blood. One of the many factors contributing to T2DM is a genetic anomaly[26]. In 2011, several studies found that about 36 genes were connected to an elevated risk of T2DM. Due to these hereditary variables, only 10.0% of T2DM cases are clinically present[26]. Table 4 lists the genes that are susceptible to T2DM[29].

Due to its function in adipose tissue and lipid metabolism, the peroxisome proliferator-activated receptors γ (PPARγ) gene is crucial for study[30]. The PPARγ gene's (Pro) function lowers insulin sensitivity while simultaneously raising the risk of T2DM[30]. In most populations, this gene is regarded as being prevalent[30]. At least one copy of the Pro allele is carried by 98.0% of Europeans. As a result, it probably accounts for a sizable part (25.0%) of T2DM in the Caucasian population[30].

Humans and most other mammals contain the proteins known as ATP binding cassette, subfamily C, member 8 (ABCC8)[31]. Sulfonylurea receptor 1 (SUR1) protein is made with the help of this gene[31]. This protein and the Kir6.2 sub-unit, which is encoded by KCNJ1, are components of the ATP-sensitive potassium channel, which participate in a wide range of physiologic responses, such as controlling the release of insulin and glucagon from the beta cells of the pancreas[31]. Insulin secretion and potassium channel function can both be impacted by a gene abnormality[31], finally leading to T2DM. Intriguingly, the distance between ABCC8 and KCNJ11—which is only 4.5 KB—is close to that of the INS gene[31]. *ABCC8 (Ala) and KCNJ11 (Lys)* gene variants have been linked to T2DM[30].

A ubiquitously expressed intracellular calcium-dependent cysteine protease known as calpain 10, which is prevalent in humans, is encoded by the CAPN10 gene[32]. An intrinsic adenine (A) to glycine (G) mutation at position 43 of a haplotype that was previously associated with T2DM appears to be important in CAPN10 transcription[32]. According to physiological research, the differences in chaplain 10 activities' effects on insulin secretion increase the risk of T2DM[32]. Studies from various ethnic groups suggest that Mexican American communities may be considerably more likely than Caucasian populations to have an increase in T2DM risks because of this locus[32].

COST OF DIABETES

Diabetes economic expenses in the US rose by 26.0% between 2012 and 2017, after accounting for inflation, because of rising diabetes prevalence and per-person costs[33]. The population aged 65 and older is most affected by the rise in diabetes prevalence and medical expenses, which adds to the rising financial burden on the Medicare program[33]. The estimated $327 billion total cost of diabetes diagnosis in 2017 includes $237 billion in direct medical expenses and $90 billion in lost productivity [33]. Average annual medical costs for individuals with diabetes are $16750, of which diabetes-related expenses account for $9000 of that total[33]. Medical costs for those with diabetes are, on average, 2.3 times more expensive than that for people without the disease[33]. The indirect costs of diabetes include increased absenteeism ($3.3 billion) and decreased productivity at work ($26.9 billion) for the employed population, as well as decreased productivity for those who are not in the labor force ($2.3 billion)[33]. In addition, indirect costs include the inability to work due to disease-related disability ($37.5 billion) and lost output as a result of 277000 premature deaths that can be directly linked to diabetes ($19.9 billion)[33].

TREATMENT

The course of treatment for diabetes varies from patient to patient depending on the laboratory test results, particularly the levels of blood glucose[34]. Blood glucose control is the main objective of every treatment plan to avoid associated problems[34]. The primary treatment modalities targeting T1DM are insulin therapy, oral hypoglycemic agents, exercise, and a regulation/monitoring of diet[34]. The primary goals of T2DM are weight loss and dietary advice. In the severe event where the aforementioned techniques fail to regulate blood glucose levels, oral medication will be administered [34].

Table 3 Estimated relative risk of genes that affect type I diabetes mellitus

Gene	Locus	Variant	Estimated relative risk
HLA-DQB1	6p21.3	*0201 & *0302	3-45
INS	11p15.5	Class I	1-2
CTLA4	2q31-35	Thr17Ala	1-2

CTLA4: Cytotoxic T lymphocyte-associated 4; HLA: Human leukocyte antigen; INS: Insulin.

Table 4 Estimated relative risk of genes that affect type II diabetes mellitus

Gene	Locus	Variant	Estimated relative risk
PPARγ	3p25	Pro12Ala	1-3
ABCC8	11p15.1	Ser1369Ala	2-4
KCNJ11	11p15.1	Glu23Lys	1-2
CALPN10	2q37.3	A43G 1	1-4

ABCC8: ATP binding cassette, subfamily C, member 8; PPARγ: Peroxisome proliferator-activated receptors γ.

CONCLUSION

Diabetes has been associated with significant financial loss for the families that are affected. It has also been associated with severe complications which could leads to death. l. T1DM and T2DM are the two types of diabetes mellitus. The former is more prevalent among children, whereas the latter is more prevalent among adults. However, there are risk factors that have been identified in children that could lead to the development of T2DM and have a negative impact on their health. Diabetes is known to cause other severe complications in patients, resulting in even more misery and premature death. Individuals' chances of developing diabetes are also affected by their race, ethnicity and lifestyle. Perhaps this is related to the social and economic factors among these races. In people suffering from this disease, fortunately, interventions as well as treatment options are available.

FOOTNOTES

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MINIREVIEWS

Advances in the mechanism of action of metformin in pituitary tumors

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Abstract

Pituitary tumors are common intracranial tumors, but when faced with drug-resistant or aggressive tumors, existing medical measures may not provide good control, leading to progression and deterioration. Metformin, a traditional hypoglycemic drug, has recently been discovered to have multiple functions including antitumor effects. There have been studies on the mechanism of metformin for the treatment of pituitary tumors, but it is uncertain whether it will provide new adjuvant or alternative therapies for the treatment of these tumors. We analyzed the potential mechanisms of action of metformin with respect to the inhibition of pituitary tumor growth and hormone secretion by reviewing the available literature.

Key Words: Metformin; Pituitary tumor; Mechanism; Treatment; Study; Review

Core Tip: Pituitary tumors are common intracranial tumors, but when faced with drug-resistant or aggressive tumors, existing medical measures may not provide good control, leading to progression and deterioration. Metformin, a traditional hypoglycemic drug, has recently been discovered to have multiple functions including antitumor effects. There have been studies on the mechanism of metformin for the treatment of pituitary tumors, but it is uncertain whether it will provide new adjuvant or alternative therapies for the treatment of these tumors. We analyzed the potential mechanisms of action of metformin on the inhibition of pituitary tumor growth and hormone secretion by reviewing the available literature.

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INTRODUCTION

Pituitary adenoma is a common intracranial tumor, accounting for approximately 10% to 15% of neurological tumors, and its incidence is second only to glioma and meningioma[1-5]. Pituitary tumors originate in the anterior pituitary gland and are usually benign lesions with slow growth. They are classified according to their size: Pituitary microadenomas (< 1 cm in diameter), macroadenomas (≥ 1 cm in diameter) and giant adenomas (> 4 cm in diameter)[6,7]. According to their different growth sites, they can secrete different hormones such as growth hormone (GH), prolactin (PRL), adrenocorticotropic hormone (ACTH), and thyrotropin, or they can be nonfunctional adenomas that do not secrete hormones. Clinical manifestations mainly include the mass effect of the tumor and endocrine symptoms due to hyper- or hypofunction of the pituitary or target gland[8-10]. Although most pituitary tumors can be controlled by drug therapy, surgery, and radiation therapy, some of these tumors may become drug resistant or recurrent, or even invade surrounding tissue structures, which may make treatment more difficult or prevent effective control of the tumor to achieve the desired therapeutic goals. A such, it is critical to find alternative therapies or new technologies to control the growth and hormone secretion of resistant or invasive pituitary tumors.

Metformin is a drug widely used in the treatment of diabetes mellitus, given its ability to reduce liver damage, promote insulin production, and increase insulin sensitivity and peripheral glucose utilization. In recent years, a number of *in vitro* and *in vivo* studies and reviews have shown that metformin has the effect of inhibiting the growth of various types of tumors or cancers, including neuroendocrine tumors, through various mechanisms[11-19]. This indicates that metformin may help to reduce the possibility of tumor or cancer occurrence and provide treatment benefits in patients. Although there are some epidemiological data demonstrating the relationship between metformin and risk reduction in patients suffering from multiple tumors or cancers, the role of metformin in cancer treatment is not yet fully clear[3,11,17,20-23]. Here, we review the available literature on the role of metformin in pituitary tumors and discuss the potential mechanisms of action of this drug with respect to the treatment of these tumors (Figure 1).

MECHANISM OF ACTION STUDY

Mitochondria-mediated pathways

The B-cell lymphoma 2 (Bcl-2) family is a key regulatory member of the mitochondrial-mediated apoptotic pathway, activating the downstream death program, which in turn leads to caspase-3 enzyme cleavage and ultimately apoptosis, characterized by a decrease in mitochondrial membrane potential (MMP).

In one study, decreased MMP, increased expression of pro-apoptotic proteins, and decreased expression of anti-apoptotic proteins were observed in GH3 cells treated with metformin. This finding suggests the involvement of the mitochondria-mediated apoptotic pathway, indicating that metformin may induce apoptosis in GH3 cells by downregulating the Bcl-2/BAX ratio and inducing caspase-3 cleavage activation and thus achieve anti-tumor effects[24]. In another study, metformin was observed to inhibit the proliferation of MMQ, cells and similar mitochondria-mediated apoptosis and experimental results were observed[25].

Another study observed that metformin inhibited the proliferation of ACTH-secreting mouse pituitary cortical dystrophoma cells AtT20, promoted apoptosis, and reduced ACTH secretion, but did not prevent progression of the cell cycle. Metformin-induced apoptosis was accompanied by an increase in caspase-3 activity, while metformin downregulated the anti-apoptotic protein Bcl-2 but upregulated the pro-apoptotic protein BAX, suggesting the involvement of a mitochondria-mediated apoptotic pathway[26]. However, a different study suggested that metformin does not increase apoptosis in GH3 pituitary tumor cells, possibly due to the experimental design or the nutritional environment used; this effect of metformin needs further investigation[27].

AMPK-mediated related pathways

In one study, adenosine monophosphate activated protein kinase (AMPK) was found to mediate growth inhibition or apoptosis of many types of tumor cells[2,28-30]. As metformin is an activator of the AMPK pathway[2], it has been suggested that it activates AMPK by restricting complex I in the mitochondrial respiratory chain, generating cellular energy stress, and thus activating AMPK[27,31-33] and indirectly

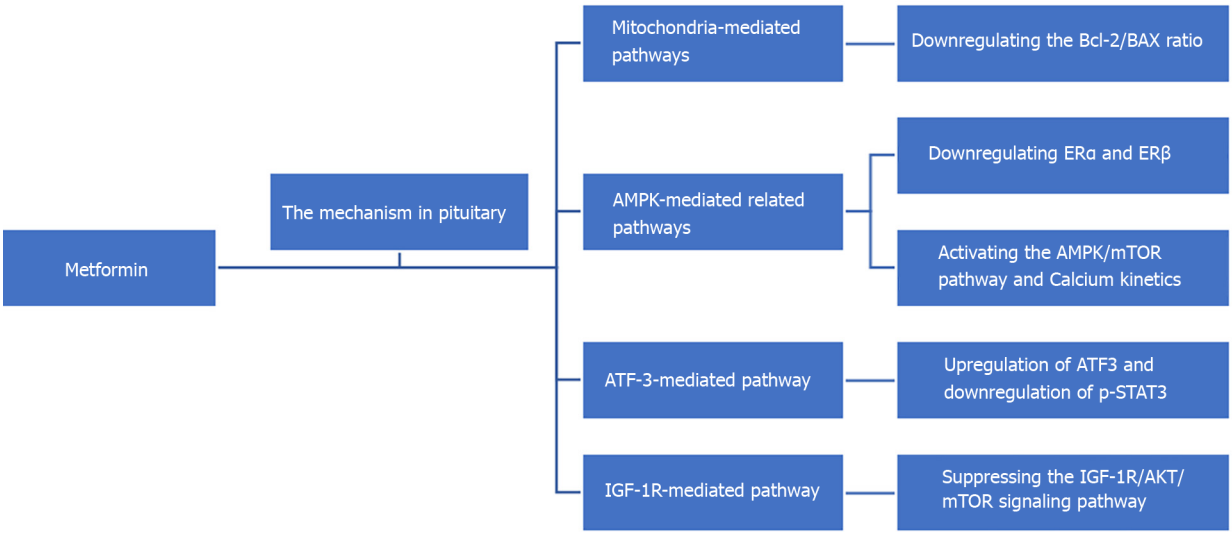

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Figure 1 Potential mechanisms of metformin in the treatment of pituitary tumors. AMPK: Adenosine monophosphate activated protein kinase; ATF: Activating transcription factor; AKT: Protein kinase B; BAX: Bcl-associated X, IGF: Insulin-like growth factor; mTOR: Mammalian target of rapamycin.

by increasing the [AMP]:[ADP] ratio[28]. However, it is not clear what the role of metformin may be in pituitary tumors, raising concerns about its mechanism of action in pituitary tumor cells.

Previous work has noted sex-dependent effects of mesenchymal epithelial transition (MET) on serum PRL levels, suggesting that the hypothalamic-pituitary-gonadal axis may be a target of metformin. One study investigated the AMPK agonist by measuring AMPK phosphorylation in human primary prolactinoma samples using bromocriptine (BC)-sensitive MMQ cells and BC-resistant GH3 cells and their xenografts as models. The role of MET in prolactinoma and the downstream effectors were investigated. It was proposed that AMPK signaling is inhibited in D2R-positive BC-resistant human prolactinomas. The AMPK activator MET inhibited the proliferation of BC-sensitive (MMQ) and drug-resistant (GH3) prolactinoma cells. It has also been shown that bromocriptine resistance is associated with downregulation of AMPK activity and high estrogen receptor (ER) expression, and that MET downregulates ERα and ERβ by activating the AMPK signaling pathway and inhibits prolactinoma growth and PRL secretion[34]. Overall, MET inhibits prolactinoma growth and PRL secretion by activating the AMPK signaling pathway.

It has been shown that metformin enhances phosphorylated AMPK expression and decreases phosphorylation levels of mammalian target of rapamycin (p-mTOR) expression in MMQ cells. Additionally, compound C, an AMPK inhibitor, reduces the inhibitory effect of metformin on p-mTOR expression. It has been suggested that metformin activates the AMPK/mTOR pathway, which may be part of the mechanism to inhibit MMQ cell proliferation and induce apoptosis and G0/G1 phase block [25]. Meanwhile, metformin significantly increased the levels of phosphorylated AMPK, phosphorylated protein kinase B, and phosphorylated mTOR in AtT20 cells in a dose-dependent manner, demonstrating that metformin activated AMPK and inhibited mTOR in AtT20 cells, suggesting that the activation of AMPK/mTOR signaling pathway may be related to metformin-induced proliferation inhibition and apoptosis promotion in AtT20 cells. However, it remains to be verified whether the activation of AMPK is related to the reduction of hormone secretion[26].

However, another study found that in GH-secreting PitNET cells, metformin induced GH3 cells to inhibit the target of epidermal growth factor (EGF) -induced mTOR-p70S6 6 kinase signaling pathway. As a potential mechanism, it was suggested that downstream EGF receptors were incorporated into AMPK substrates, indicating that membrane receptors are direct targets and may be involved in mediating their inhibitory effects on cell growth. In this study, the presence of AMPK targets, including cell surface receptors in GH3 cell membranes, was demonstrated using protein fractions[27].

Calcium has been reported to be a relevant second messenger for pituitary cell physiology. It has been shown that the effect of metformin on PitNET may involve AMP-activated protein kinase-dependent calcium kinetics, thereby altering cell viability. However, the altered calcium kinetics induced in different pituitary tumor cells are variable, suggesting that metformin inhibits different types of pituitary tumor cells differently, and that the observed altered calcium kinetics appear to be related to hormone secretion[35].

Activating transcription factor-3-mediated pathway

Activating transcription factor 3 (ATF3) is a stress response transcription factor belonging to the ATF/CREB family. In one study, ATF3 was found to be upregulated by metformin, and its knockdown

significantly reduced metformin-induced apoptosis, suggesting that ATF-3 may mediate the pro-apoptotic effect of metformin. The inhibitory effect of compound C on AMPK did not alter the inhibitory effect of metformin on STAT3 activity, suggesting that metformin may reduce GH secretion by inhibiting non-AMPK-dependent STAT3 activity. Metformin also significantly inhibited cell proliferation and GH secretion in primary human growth hormone-secreting pituitary adenoma (GH-PA) cells. Upregulation of ATF3 and downregulation of p-STAT3 were also demonstrated in xenografts. It was revealed that metformin inhibited the growth of somatic dystrophic adenoma cells both *in vitro* and *in vivo* through ATF-3-mediated pro-apoptotic effects. These findings suggest that metformin is a potentially promising therapeutic agent for the treatment of GH-PA[24].

Insulin-like growth factor -1R-mediated pathway

Insulin-like growth factor (IGF) -1R is an important growth factor receptor that activates the downstream phosphatidylinositol 3-kinase (PI3K)/protein kinase B (AKT)/mTOR pathway upon binding to IGF-1. The overactivation of this pathway is associated with tumor development. It has been observed that IGF-1R, p-AKT (S473), and p-ERK levels decreased with increasing metformin concentration after treatment. The IGF-1R inhibitor PPP inhibited MMQ cell proliferation, suggesting that metformin may inhibit cell proliferation by inhibiting the IGF-1R pathway in MMQ cells[25]. These results suggest that metformin may inhibit cell proliferation by inhibiting the IGF-1R pathway in MMQ cells.

In another study, metformin decreased IGF-1R expression, AKT (S473) phosphorylation, and mTOR (Ser2448) phosphorylation, which inhibited AtT20 cell proliferation, Moreover, PPP (an IGF-1R inhibitor) significantly inhibited AtT20 cell proliferation in a dose-dependent manner, suggesting that IGF-1R plays a role in tumor progression. Taken together, these findings suggest that metformin may inhibit AtT20 cell proliferation by suppressing the IGF-1R/AKT/mTOR signaling pathway[26].

DISCUSSION

It is known from the above studies that there may be multiple pathways for the effect of metformin on pituitary tumors, but the complete mechanisms of these different pathways are not entirely clear. Moreover, the findings and opinions on the same pathway are not consistent. The effects of metformin have been attributed to its actions on different cells or in different environments. Indeed, it has been pointed out that the effect of metformin at the cellular level depends on the metabolic characteristics and metabolic demands of the cells, and the tumor microenvironment may influence this response. Pyruvate metabolism branching points are likely to play a major role in the variability of the cellular response to metformin, a role supported by significant differences in pyruvate dehydrogenase complex expression levels between myogenic cells and pituitary tumor cells[36]. Research conducted *in vitro* and in and clinical trials are still limited or unavailable; as such, more evidence is needed to verify the accuracy of these ideas.

There is *in vitro* evidence suggesting that it may not be feasible to achieve high concentrations of metformin in humans[37,38]. The observation that the prevalence of various tumor types is lower in patients with type 2 diabetes on regular metformin doses and that serum concentrations of metformin are much lower than those that inhibit cancer cells *in vitro* raises the possibility that the mechanism of tumor prevention *in vivo* with regular therapeutic doses of metformin may be largely indirect and related to metformin ameliorating such metabolic or hormonal abnormalities such as obesity, hyperglycemia, and hypertension. It is also important to consider that there may be physiological metabolic differences between rat pituitary tumor cell lines and human pituitary tumor cell lines, among others.

Despite these studies, metformin has not been formally used as a clinical treatment for pituitary tumors. There have been case reports of reduced prolactin levels and tumor size in 2 patients treated with a combination of bromocriptine and metformin, whereas bromocriptine alone was not sufficient to reduce prolactin levels or slow tumor growth[39]. In another case report, the combination of bromocriptine and metformin reduced prolactin levels and tumor size. In a third case report, the combination of metformin and capsaicin did not show consistent inhibition of serum prolactin levels in either the short- or long-term in 10 patients with prolactinoma resistant to capsaicin[40]. Additional studies have evaluated the effects of metformin on cell viability and hormone secretion when combined with other agents; for example, metformin/somatostatin (SSA) analog combination therapy did not increase the effectiveness of SSA monotherapy[34]. Metformin/SSA combination therapy did not increase the effectiveness of SSA monotherapy, but did appear to enhance the role of octreotide in GHomas, and MET + BC significantly inhibited PRL secretion, further reducing tumor growth and serum PRL levels in xenografts when compared to BC treatment alone[35]. However, in the face of metformin treatment, the tumor growth and serum PRL levels in xenografts were further reduced.

The heterogeneity among patients with pituitary tumors and the diversity of drug treatment options add to the complexity of disease treatment, and further studies are needed to demonstrate whether treatment with metformin alters the risk of pituitary tumor morbidity and mortality and to determine

the dose and duration of treatment and the effect when combined with other drugs. It is also important to consider whether it is reasonable to use metformin to treat pituitary tumors in patients without diabetes and to pay mind to the potential side effects or complications of using different concentrations of metformin in humans. Attention to these possible issues could help to improve the management of pituitary tumor patients in a more individualized manner. Given the available data, the use of metformin may be a promising and clinically relevant option for patients with pituitary tumors. Further studies are needed to confirm metformin's clinical relevance as an adjuvant or novel therapy and to further develop a comprehensive understanding of the potential antitumor mechanisms of this drug in the treatment of pituitary tumors.

CONCLUSION

Metformin, a traditional hypoglycemic drug, has recently been discovered to have multiple functions including antitumor effects. There have been several studies on the mechanism of metformin for the treatment of pituitary tumors, but it remains to be investigated whether it will be incorporated as an alternative therapy for the treatment of these tumors.

FOOTNOTES

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SYSTEMATIC REVIEWS

Pulmonary cytomegalovirus infection: A case report and systematic review

Awotar Kanika, Jonathan Soldera

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Abstract

BACKGROUND

Cytomegalovirus (CMV) is a common virus that can cause the first infection in childhood or adolescence and reactivate later in life due to immunosuppression. CMV pneumonia is a rare illness in immunocompetent patients but is one of the most significant opportunistic infections in immunocompromised patients.

AIM

To report a case and review published cases of pulmonary CMV infection in both immunocompromised and immunocompetent patients.

METHODS

We conducted a systematic search on the MEDLINE (PubMed) database, without date or language restrictions, to identify relevant studies using Medical Subject Headings and Health Science Descriptors. We manually searched the reference lists of the included studies. Simple descriptive analysis was used to summarize the results.

RESULTS

Our search identified 445 references, and after screening, 43 studies reporting 45 cases were included in the final analysis, with 29 (64%) patients being immunocompromised and 16 (36%) being immunocompetent. Fever (82%) and dyspnea (75%) were the most common clinical findings. Thoracic computed tomography showed bilateral ground-glass opacities, a relevant differential diagnosis for severe acute respiratory syndrome coronavirus 2 infection. The majority of patients (85%) received antiviral therapy, and 89% of patients recovered, while 9% of patients died.

CONCLUSION

CMV pneumonia should be considered as a differential diagnosis for coronavirus disease 2019 pneumonia, especially in immunocompromised patients. Clinicians should be aware of the clinical presentation, management, and outcomes of CMV

pneumonia to guide appropriate treatment decisions.

Key Words: Cytomegalovirus; Immunocompromised; Immunocompetent; Severe acute respiratory syndrome coronavirus 2; Coronavirus disease 2019; Ganciclovir

Core Tip: The paper reports a case of disseminated cytomegalovirus (CMV) infection in an immunocompetent patient who presented with cough, dyspnea, high-grade fever, and jaundice. The patient was diagnosed with CMV pneumonia after developing sepsis and being admitted to the intensive care unit. The study conducted a systematic search on the MEDLINE database to identify published cases of pulmonary CMV infection in both immunocompromised and immunocompetent patients. The search identified 43 studies reporting 45 cases, with 29 (64%) patients being immunocompromised and 16 (36%) being immunocompetent. Fever and dyspnea were the most common clinical findings, and thoracic computed tomography showed bilateral ground-glass opacities. The majority of patients received antiviral therapy, and 89% of patients recovered, while 9% of patients died. The study highlights that CMV pneumonia should be considered as a differential diagnosis for coronavirus disease 2019 pneumonia, especially in immunocompromised patients, and clinicians should be aware of the clinical presentation, management, and outcomes of CMV pneumonia to guide appropriate treatment decisions.

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INTRODUCTION

Cytomegalovirus (CMV) is a DNA virus that belongs to the herpesviridae family and shares similarities with other herpes viruses. In immunocompetent adults, CMV infection is usually asymptomatic and causes mild mononucleosis-like syndrome, typically in childhood or adolescence. However, CMV can cause severe disease and pneumonia in immunocompetent individuals, albeit rarely[1,2]. CMV infection may lead to severe viral pneumonitis in immunocompromised patients, such as those with autoimmune deficiency syndrome (AIDS), allogeneic bone marrow transplantation recipients, or those on immunosuppressive drugs or high-dose steroids. The incidence of CMV infection is approximately 25%-30% in recipients of hematopoietic stem cell transplantation[3]. The gastrointestinal tract and central nervous system are the most frequent sites of severe CMV infection. CMV was one of the three most common causes of severe viral community-acquired pneumonia (CAP), along with influenza and adenovirus. However, this has changed with the emergence of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in 2020[4]. The pulmonary manifestations of CMV infection may vary from a dry cough to severe interstitial pneumonia, with patients presenting with diffuse pulmonary infiltrates resembling a ground glass appearance. The diagnosis of CMV pneumonia is based on radiological patterns and serology (CMV IgM antibody) or polymerase chain reaction (PCR)[4]. In 1968, the first case of CMV CAP was reported by Carlstorm and colleagues in their case series of CMV infection in immunocompetent hosts[5]. CMV CAP in immunocompetent hosts presents as prolonged fever and interstitial infiltrates on chest X-ray that resolved slowly over 6 wk. Patients with CMV CAP present with relative lymphopenia, atypical lymphocytes, and mildly elevated serum transaminases. Primary CMV infection persists for life and is generally acquired through close physical contact involving direct inoculation with infected cells or body fluids. The spread of viral infection is through coughing, direct contact with body fluids such as blood, urine, feces, semen, vaginal fluid, and breast milk, or *via* mucous membranes, including the mouth or genitals. CMV infection following transplantation can be acquired if the transmission is from the organ from a CMV-seropositive donor. Mothers infected with CMV during pregnancy may transmit this infection to their newborn baby, leading to congenital CMV. CMV infection is one of the leading causes of miscarriage[1,6]. Babies with congenital CMV sometimes may be healthy for months or years after birth but may have late occurring signs such as hearing loss, and develop vision problems and developmental delay. Latent CMV can reactivate and replicate rapidly when the immune system is suppressed. It can lead to high levels of CMV viremia, and infection of multiple organ systems can cause severe illness such as retinitis, colitis, hepatitis, pneumonia, or encephalitis. Fatal CMV pneumonia is more common in patients who have received marrow transplants than those who received transplant of solid organs like the lung, heart, liver, or kidney[7,8]. CMV accentuates the sepsis-induced immunologic effects, leading to an increase in the risk for secondary

infections. CMV infection in critically ill patients is associated with prolonged ventilator support, nosocomial infections, prolonged hospital/intensive care unit (ICU) stay, and increased mortality rates [9].

As the coronavirus disease 2019 (COVID-19) pandemic continues and becomes an endemic, it is crucial to recognize that not all clinical and radiological presentations are solely attributable to COVID-19[10]. Therefore, diagnostic differentiation is essential, and ground-glass opacities (GGOs) must be evaluated in conjunction with other imaging findings, laboratory tests, and clinical features to reach a definitive diagnosis. CMV pneumonia can be diagnosed by detecting the virus in serum and/or respiratory samples such as bronchoalveolar lavage (BAL) or tracheal aspiration[10]. Quantitative real-time PCR (qRT-PCR) can be utilized to measure viral loads in blood and BAL fluid[11]. Lung biopsy histopathology is considered the gold standard for diagnosing pulmonary CMV infections, with the presence of CMV inclusion bodies (owl's eye) in biopsy specimens being confirmatory of lung infection [12]. However, the diagnostic yield of lung biopsy for diagnosing lung CMV infections can vary as inclusions may not always be visualized. Immunohistochemical (IHC) staining for CMV in cytological specimens of bronchial washing fluid can also detect CMV[13,14].

The first-line treatment for CMV disease is intravenous ganciclovir and its prodrug, oral valganciclovir, which inhibits viral deoxyribonucleic acid (DNA) polymerase, thereby interfering with DNA elongation. Mild disease in immunosuppressed patients may be treated with oral valganciclovir, whereas severe illness requires initial treatment with intravenous ganciclovir or foscarnet at full doses (adjusted for renal function)[15]. Treatment at full doses should be continued until symptom resolution and blood antigenemia (or DNAemia) clears. Adjuvant treatment with intravenous immunoglobulin or CMV hyper-immunoglobulin is recommended in immunocompromised patients and may be used in cases of severe CMV disease and hypogammaglobinemia[12].

This study aimed to report a case of disseminated CMV in an immunocompetent patient, and systematically review published cases of pulmonary CMV infection in both immunocompromised and immunocompetent patients.

Case report

Chief complaints: A 32-year-old man presented with a cough, dyspnea, high-grade fever, and jaundice.

History of present illness: The patient had no significant medical history and was not taking any medication. Physical examination revealed a temperature of 39.5°C, tachypnea, icteric sclera, and hepatosplenomegaly. He had no skin rash or lymphadenopathy. The initial blood tests showed pancytopenia, elevated liver enzymes, elevated bilirubin, and hypoalbuminemia. CT of the thorax showed GGOs, while CT of the face showed sinusitis, raising suspicion of an infectious etiology.

History of past illness: The patient had no significant past medical history.

Personal and family history: No significant personal or family history was reported.

Physical examination: The patient presented with a temperature of 39.5°C, tachypnea, icteric sclera, and hepatosplenomegaly. He had no skin rash or lymphadenopathy.

Laboratory examinations: Complete blood count revealed a platelet count of 87000/mm^3, hemoglobin level of 8.2 g/dL, and leukocyte count of 4830/mm^3. Liver function tests showed alkaline phosphatase of 1174 U/L, gamma-glutamyl transferase of 804 U/L, aspartate aminotransferase of 403 U/L, total bilirubin of 17.2 mg/dL, albumin of 1.7 g/dL, and international normalized ratio of 1.11. Autoimmune antibody testing for fluorescence antinuclear antibody was negative. COVID-19 antigen swab test was negative.

Imaging examinations: After a liver biopsy, the patient's results were suggestive of drug-induced liver injury, and subsequent immunochemistry testing returned negative results for CMV. Magnetic resonance imaging (MRI) of the abdomen showed a liver with enlarged dimensions, regular contours, and heterogeneous signal intensity, with predominance of hyper signal in the T2-weighted sequences, suggestive of an inflammatory process (hepatitis), and splenomegaly and pancreatic edema suggestive of pancreatitis. CT of the thorax showed GGOs (Figure 1), while CT of the face showed sinusitis.

Final diagnosis: The patient's clinical condition worsened, and he developed hypotension and sepsis, requiring admission to the ICU. Broad-spectrum antibiotics were started, and he was investigated for possible Wegener's granulomatosis. However, auto-antibodies were negative and his final diagnosis was disseminated CMV infection, confirmed by the high viral load of 325192.5 copies/mL.

Treatment: The patient was started on ganciclovir therapy.

Outcome and follow-up: After 6 wk of treatment, the patient recovered completely from his symptoms, achieving a sustained undetectable viral load.

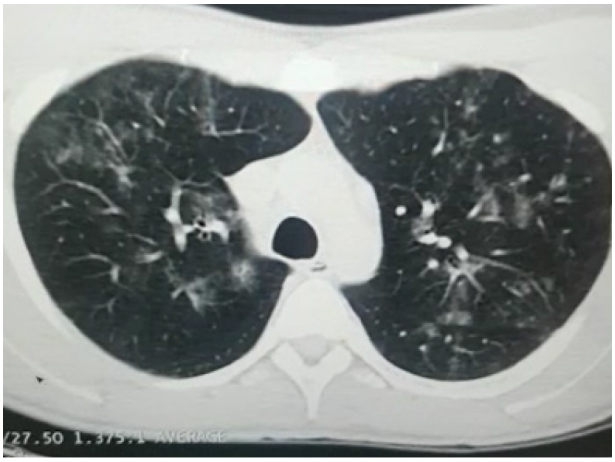

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Figure 1 Computed tomography of the thorax showing ground glass opacities.

MATERIALS AND METHODS

This study followed the recommendations outlined in the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines[16].

Data sources

The electronic database MEDLINE (PubMed) was searched using the terms described in the Supplementary material. The searches were conducted in September and October 2022, with no date of publication restrictions and language restricted to English. References of included studies were screened for relevant records, and the reference lists of the retrieved studies were submitted to a manual search.

Inclusion and exclusion criteria

Case report or case series studies were eligible for selection. If there was more than one study published using the same case, the most recent study was selected for analysis. Studies published only as abstracts were also included, as long as the data available made data collection possible. Studies written in languages other than English were excluded. Studies having other co-existing causes of pneumonia were excluded from our study, for example, superimposed bacterial, parasitic, or fungal infections in existing CMV pneumonia, and other lung pathologies.

Study selection and data extraction

Titles were screened initially to select the cases of pulmonary complications of CMV infection and filter out non-relevant studies. Then, abstracts of chosen studies were read to select potentially relevant papers. The third step was the analysis of the full-length papers, and those which were not case reports of pulmonary CMV were filtered out. Data was extracted on the characteristics of the subjects and the outcomes measured from each eligible study. A table of extracted data on eligible studies was made in order to measure and identify patterns.

RESULTS

Using the search strategy, a total of 435 references were retrieved. After reviewing titles, 232 studies were found to be relevant for our topic and 203 studies were excluded. By analyzing abstracts, 172 studies were found to be potential relevant papers for our topic and therefore 60 studies were excluded. After reading and analyzing full length papers, 43 studies with 45 case reports of pulmonary CMV infection were included. The data of 45 case reports was extracted and prepared in Table 1 to measure and identify the patterns to get the results to reach a conclusion. Figure 2 shows the PRISMA search strategy. Every study included was a case report.

The baseline features are described in Table 2 and Table 3 for the 45 patients who were included for data extraction. All patients were diagnosed with CMV pneumonia. The majority of patients were males (58%) and in the age group of 16-45 years (55.6%). The most common symptoms reported were fever (82%), dyspnea (76%), and cough (53%). Respiratory distress was observed in 58% of the patients. Almost two-thirds of the patients (64%) were immunocompromised. Radiographic findings were reported in 71% of the patients by chest X-ray and 69% by CT. Blood/serum was the most commonly used method for serology testing (89%), and bronchoalveolar fluid was used in 45% of the cases.

Table 1 Summary of systematically reviewed clinical cases of cytomegalovirus pneumonia

Ref.	Age	Sex	Clinical findings	Immune status	Radiographic findings	Serology	Immunohistochemistry & biopsy	Treatment	Out-come
Luís *et al*[22], 2021	42	M	Fever, headache, odynophagia, bilateral otalgia	Immunocompetent	CXR – B/L infiltrates; Thoracic CT – B/L GGO	Blood – CMV PCR positive; BAL fluid – CMV PCR positive		Ganciclovir and valganciclovir	Recovery
Balakrishnan *et al* [23], 2022	41	M	Fever, cough, weight loss	Immunocompromised; chronic glomerulo- nephritis, IgA nephropathy; on immunosup-pressive drugs	CXR – B/L infiltrates; Thoracic CT – B/L GGO, patchy consolidation, nodular opacities	Blood – CMV PCR positive; BAL fluid – CMV PCR positive		Valganciclovir	Recovery
Basinger *et al*[24], 2022	70	M	Rapid decline in general condition, resp. distress	Immunocompromised; a history of allogenic hematopoietic stem cell transplant	Rapidly progressive bilateral pulmonary nodules	Not done	Post mortem cytopatholog. Change, consistent with CMV infection, confirmed by IHC	Not initiated	Died
Gonçalves *et al* [2], 2018	29	M	Fever, headache, malaise, cough, thoracic pleuritic pain	Immunocompetent	Thoracic CT showed bilateral infiltrates	Blood – positive for CMV IgG and IgM; BAL – CMV PCR was positive		Ganciclovir and valganciclovir	Recovery
Wong *et al*[25], 2022	37	M	Fever, cough, dyspnea	Immunocompromised; X-linked agammaglobulinemia is a hereditary immune disorder		CMV positive		Antiviral and immune globulin therapy	Recovery
Gangemi *et al* [26], 2021	72	M	Non-healing buccal ulcer, fever, acute hypoxic respiratory failure, worsening odynophagia, weight loss	Immunocomromised; oropharyngeal Ca in remission	Chest X-ray – patchy opacities of B/L lung fields; Thoracic CT – bilateral upper and lower lobe consolidations, B/L pleural effusions	Positive for both CMV IgG and IgM		Ganciclovir and valganciclovir	Recovery
Patil *et al*[27], 2020	23	F	Worsening dyspnea, high grade fever, dry cough	Immunocompetent	Chest X-ray – mild bilateral interstitial infiltrates with small bilateral pleural effusions; CT chest - worsening of bilateral interstitial infiltrates	BAL CMV PCR and blood CMV PCR positive		Ganciclovir and valganciclovir	Recovery
Alyssa *et al*[28], 2017	63	F	Fever, hypotension, dyspnoea on exertion, hypoxemia, weakness	Immunocompromised; diagnosis of dermatomyositis - history of prolonged use of glucocorticoids and treatment with rituximab	CT chest - bilateral GGOs in a mosaic distribution and consolidations of B/L lower lobes	CMV DNA PCR quantitation in whole blood was positive and shell-vial culture for CMV positive		Ganciclovir and valganciclovir	Recovery
Fragkiadakis *et al* [29], 2018	36	F	Fever, respiratory distress	Immunocompromised; undergone multiple transfusions, and splenectomy was done for homozygous β-thalassemia	CT chest demonstrated pneumonitis	Serology and molecular blood testing reports – CMV infection and viremia		Ganciclovir	Recovery
Waqas *et al*[30], 2019	36	M	Fever, cough, malaise	Immunocompetent	CXR – B/L infiltrates	Diagnosed with CMV infection		Ganciclovir	Recovery
Xie *et al*[31], 2021	22	M	Fever, progressive dyspnea,	Immunocompromised; newly	Chest CT – extensive GGOs of	CMV quantitative PCR		Ganciclovir	Recovery

			dry cough	diagnosed HIV infection	bilateral lungs with multiple cavity lesions in the left upper lung	positive			
Al-Eyadhy *et al* [32], 2017	12	M	Tachycardia, tachypnea, fever, severe ARDS with multi-organ failure	Immunocompetent; CMV infection associated morbidity and mortality among immune-competent children	CXR and chest CT – ARDS features	CMV PCR positive in blood	HPE of lung biopsy CMV positive	Ganciclovir	Recovery
Reesi *et al*[33], 2014	3	M	Fever, dyspnea	Immunocompromised; acute lymphoblastic leukaemia on chemotherapy	CXR - pulmonary infiltrates; CT chest - diffuse GGOs of B/L lung fields, few pleural-based nodules	BAL CMV PCR was positive; CMV IgG and IgM positive		Ganciclovir and valganciclovir	Recovery
Cunha *et al*[34], 2008	64	M	"Flu-like illness", fever, myalgias, progressive dyspnoea, and required mechanical ventilation	Immunocompetent; slowly improved over 14 d and was eventually extubated	Chest X-ray showed B/L interstitial markings that rapidly progressed over 24 h	Initially IgG, IgM and CMV PCR negative; 10 d later, IgG, IgM, and CMV PCR were positive	BAL cytology was negative for viral inclusions	Did not receive CMV antiviral therapy	Recovery
Demirkol *et al* [35], 2018	2	M	Respiratory distress, fever, multiple organ dysfunction secondary to sepsis	Immunocompetent; developed necrotizing pneumonia	Thoracic CT – features of necrotising pneumonia	Serological tests indicated that the patient had CMV reactivation	Excised lung tissue, features of CMV infection	Ganciclovir	Recovery
Margery *et al*[36], 2009	43	F	Fever, dyspnoea	Immunocompetent	Thoracic CT – diffuse GGOs	Anti-CMV IgM and PCR detection of viral DNA in serum		Not treated	Recovery
Bansal *et al*[37], 2012	45	F	Nausea and vomiting. CMV infection can present with only atypical symptoms in liver transplant patients	Immunocompromised; liver transplant due to anti- tubercular drug induced acute liver failure	CXR showed B/L infiltrates	Testing of CMV viral load showed a viral load of 9640 copies/mL		Ganciclovir	Recovery
Sunnetcioglu *et al* [38], 2016	24	M	Cough, fever dyspnoea, haemoptysis, shortness of breath, and was intubated	Immunocompromised; on immunesuppressive therapy for polyarteritis nodosa	Chest X-ray showed right-sided opacity in the middle and lower lung zones Thoracic CT showed B/L alveolar opacity	Positive test for serum CMV IgM antibodies		NA	NA
Liatsos *et al*[39], 2017	40	F	Acutely ill with fever, dry cough, and mild shortness of breath	Immunocompromised; β-thalassemia major with splenectomy, regularly transfused with packed and leukocyte-depleted red blood cells	Thoracic CT - B/L interstitial lung infiltrates and small nodules marked toward the lower lobes, with a few ground-glass areas and bilateral pulmonary effusions	Positive RT-PCR for CMV in both blood and BAL		Ganciclovir and valganciclovir	Recovery
Wickramasinghe *et al*[40], 2022	32	M	Headache, fever, cough, and shortness of breath. The patient was in respiratory distress, shifted to ICU and electively intubated	Immunocompromised; Tuberculosis meningitis	Chest X-ray showed left-sided consolidation. CT chest revealed lower lobe (left more than right) consolidation and nodules	Positive CMV IgM and negative IgG, suggesting acute infection		Antitubercular drugs and ganciclovir	Recovery
Barclay *et al*[41], 2011	38	F	Fever and non-specific symptoms & increasingly hypoxaemic	Immunocompetent	Thoracic HRCT showed diffuse multilobular ground glass appearance with	CMV IgM antibody was positive and CMV PCR was positive		Valganciclovir	Recovery

					peripheral nodular opacities				
Coussement *et al* [42], 2016	64	F	Fever, cough, dyspnea, hypoxemia	Immunocompromised; bilateral lung transplant for chronic obstructive pulmonary disease	Thoracic CT demonstrated bilateral infiltrates; abdominal CT showed peri-colic infiltration compatible with a recurrence of diverticulitis	CMV VL observed both in blood and BAL samples; a diagnosis of CMV pneumonitis using BAL sample; a macrophage characteristic of CMV viral infection	Resected colon revealed HPE CMV colitis, viral inclusions, and positive immunohistochemistry	Ganciclovir	Recovery
Kanhere *et al*[43], 2014	3 1/2	M	Fever, respiratory distress, hepatosplenomegaly	Immunocompromised; hemophagocytic lymphohistiocytosis		CMV IgM serology was reactive in both infant and mother		Ganciclovir	Recovery
Suresh *et al*[44], 2013	7/12	M	Cough, dyspnoea, respiratory distress, progressive increase in oxygen requirement	Immunocompetent	Chest XR -prominent bronchovascular markings	CMV IgM serology was positive and CMV PCR based on BAL was also positive		Ganciclovir and valganciclovir	Recovery
Suresh *et al*[44], 2013, Case 2	3/12	F	Cough, dyspnoea, respiratory distress, progressive increase in oxygen requirement	Immunocompetent	CXR normal	CMV IgM blood was raised; BAL positive for CMV PCR		Ganciclovir and valganciclovir	Recovery
Yu *et al*[45], 2017	64	M	Acute respiratory failure with renal failure	Immunocompromised; diabetic; severe CMV pneumonia with slow resolution or persistent viremia on treatment	Chest X-ray -predominately right lung infiltrates; chest CT showed multiple consolidative patches with air bronchograms	Positive CMV PCR in blood and BAL	Lung biopsy was done. Inclusion bodies, positive for CMV IHC	Ganciclovir and valganciclovir	Died
Tollitt *et al*[46], 2016	71	F	Hemoptysis	Immunocompromised; antineutrophil cytoplasmic antibody-associated vasculitis; on therapy with cyclophosphamide, steroids, and plasma exchange	Pulmonary CMV disease mimics pulmonary disease associated with vasculitis on CXR	BAL demonstrated positivity for CMV DNA and serum CMV PCR positive		Ganciclovir and valganciclovir	Recovery
Vetter *et al*[47], 2010	70	F	Fever, nausea, dyspnea	Immunocompromised; immunosuppressive therapy with methotrexate and prednisone for large-vessel vasculitis	Chest X-ray showed no interstitial pneumonitis; chest and abdominal CT showed no signs of inflammation	CMV IgG and IgM antibodies positive; CMV PCR positive in BAL fluid		Ganciclovir	Recovery
Snape *et al*[48], 2011	28	F	Fever, cough tender sinuses, frontal headache	Immunecompetent	CXR showed consolidation of the middle and right upper lobe; Pulmonary CT angiography revealed no pulmonary embolus and patchy consolidation of B/L lungs	Positivity for CMV IgM		Valganciclovir	Recovery
Karakelides *et al* [49], 2003	47	M	Cough, hemoptysis, weight loss	Immunocompetent	CXR and chest CECT showed a 3.5-cm cavitary mass, upper lobe of left lung and mild left mediastinal and hilar adenopathy	Transbronchial biopsy - CMV inclusions	Wedge excision of left upper lung mass; HPE -nuclear & cytoplasmic inclusions of CMV	NR	Recovery

Shimada *et al*[50], 2004	27	F	Fever	Immunocompromised; on immunosuppressive treatment for viral-associated hemophagocytic syndrome	CXR and chest HRCT – diffuse small pulmonary nodules	CMV DNA PCR was positive on bronchoalveolar lavage cells; immunoassay pp65 CMV antigen positive	Lung biopsy inclusion-bearing cells for CMV	Gancyclovir	Recovery
Simsir *et al*[51], 2001	43	M	Malaise, fever, pleuritic chest pain, epigastric pain, diarrhea, nausea, vomiting	Immunocompromised; underwent renal transplant secondary to diabetic nephropathy	CXR showed a nodule in the upper lobe of the right lung; chest CT revealed bilateral smaller pulmonary nodules	CMV antigen test was positive, with negative CMV IgG	CMV was established by fine-needle aspiration biopsy of the lung nodule	Gancyclovir	Recovery
Abbey *et al*[52], 2014	51	M	Fever, dry, cough, dyspnoea, general malaise	Immunocompromised; Crohn's disease on azathioprine; also had mild pancreatic insufficiency and bile salt malabsorption	CXR showed bilateral infiltrates in middle and lower zones; chest CT showed B/L small pleural effusions and B/L basal lung consolidation	CMV IgM positive, acute CMV infection		Ganciclovir and valganciclovir	Recovery
Belin *et al*[53], 2003	47	F	Shortness of breath, fever, stomatitis, genital ulcerations, burning sensations	Immunocompromised; severe rheumatoid arthritis, on prednisolone, methotrexate, and cyclosporine	CXR showed interstitial infiltrates in both lung bases	BAL showed CMV mRNA		Ganciclovir	Recovery
Kaşifoğlu *et al* [54], 2006	21	F	Polyarthralgias, fatigue, fever, muscle weakness, non-productive cough, dyspnea	Immunocompromised; dermatomyo-sitis, treated with azathioprine, prednisolone, and cyclosporine	Chest XR showed bilateral interstitial infiltration; chest HRCT - bilaterally ill-defined multifocal GGOs	Positivity for anti-CMV, IgM, and anti-CMV IgG antibodies and presence of CMV DNA by PCR		Ganciclovir	Recovery
Chen *et al*[55], 2010	5	M	Fever, cough, dyspnea, hypoxemia, ARDS	Immunocompetent; the patient developed ventilator-associated pneumonia, and died of burkhoderia sepsis	Chest XR – multiple parenchymal consolidations; chest XR disclosed "white lung" during the second week	Positive PCR; bronchoal-veolar and seroconversion of CMV IgM and IgG		NR	Died
Tambe *et al*[56], 2019	32	F	Fever, dyspnea, generalized rash, weakness	Immunocompromised; stage IV, classical Hodgkin's lymphoma, treated with chemotherapy	Chest CT revealed bilateral pulmonary infiltrates and bilateral pleural effusion	CMV was detected on BAL culture; serum quantitative CMV PCR was positive		Ganciclovir and valganciclovir	Recovery
Boussouar *et al* [57], 2018	47	F	Dry cough, chest pain and fever	Immunocompromised; orthotopic heart transplant and immunosup-pressive treatment was initiated with corticosteroids, cyclosporine, and mycophenolate	Chest XR - alveolar opacities with upper lobe predom-inance; chest CT revealed consolidation in the right upper lobe associated with septal thickening and multiple nodules	Blood CMV PCR, which has been undetectable	Lung biopsy showed nuclear inclusions suggestive of CMV infection; IHC showed nuclear positivity for CMV	Ganciclovir and valganciclovir	Recovery
Haddad *et al*[58], 1984	18	M	Fever, chills, non-productive cough, severe hypoxia requiring intubation	Immunocompromised; sickle cell thalassemia	Chest XR suggested early pulmonary edema and cardiomegaly	On postmortem culture of lung parenchyma, CMV grew in 5 d		NR	Died
Katagiri *et al*[59], 2008	35	F	Deterioration of lupus nephritis and received treatment with a high dose of steroid and cyclosporine	Immunocompromised; SLE with increased risk of opportunistic infection	Chest X-ray showed bilateral pleural effusion; chest CT revealed a cavitary lesion in the right middle lobe of the lung	Positive for CMV; antigenemia		Ganciclovir	Recovery

Ayyappan *et al* [60], 2006	72	M	Fever, productive cough, worsening breathlessness and tenderness in epigastrium	Immunocompromised; rheumatoid arthritis-related interstitial lung disease, on corticosteroids and cyclophosphamide	Chest XR showed bilateral consolidation; chest CT revealed cavitating masses in the right upper lobe & lingula and diffuse interstitial fibrosis	PCR assay of BAL fluid was positive for CMV	Gastric biopsy - intracytoplasmic viral inclusions consistent with CMV gastritis; transbronchial lung biopsy showed intracytoplasmic viral inclusion	Gancyclovir	Recovery
Manian *et al*[61], 1993	32	F	Fever, non-productive cough, worsening oxygenation	Immunocompetent	Chest X ray - bilateral interstitial infiltrates	Enzyme immune-assay showed that CMV IgG and CMV IgM were positive		Ganciclovir	Recovery
McCormack *et al* [62], 1998	31	M	Fever, abdominal pain, jaundice, cough, palpitations, shortness of breath with atrial fibrillation	Immunocompetent	Chest radiograph showed bilateral interstitial pulmonary infiltrates	EIA for antibodies to CMV showed a strong reaction to IgM and a weak reaction to IgG	A urine culture yielded CMV; a cytopathic effect was observed and con-firmed by immunofluorescence	Ganciclovir	Recovery
Najjar *et al*[63], 2004, Case 1	34	F	Fever	Immunocompromised; SLE with renal failure on haemodialysis	Chest XR - bilateral infiltrates; chest CT - bilateral peripheral parenchymal infiltrates and a cavitating mass in right lower lobe	A CMV antigenaemia assay was positive and CMV isolation in blood	Histological findings included numerous intranuclear and intracytoplasmic CMV inclusions confirmed by IHC	IV ganciclovir and IV IgG	Recovery
Najjar *et al*[63], 2004, Case 2	33	M	Fever, dyspnoea, worsening renal function	Immunocompromised; SLE, class IV lupus, nephritis treated with chronic steroid therapy, azathioprine, and cyclophosphamide	Chest CT revealed a right upper lobe thick-walled cavitary lesion	Serology revealed raised CMV IgM & IgG	HPE - evidence of focal interstitial fibrosis, accumulation of intraalveolar macrophages, and CMV with intracytoplasmic and nuclear inclusions in the lining alveolar cells	Gancyclovir	Recovery
Kanika *et al*	32	M	Fever, dyspneia, hypotension, jaundice	Immunocompetent	MRI showed hepatitis and pancreatitis; CT showed GGO	Serum PCR with a high viral load	Liver biopsy suggestive of drug induced liver injury and immunochemistry negative for CMV	Ganciclovir	Recorvery

B/L: Bilateral; GGOs: Ground glass opacities; CT: Computed tomography; ARDS: Acute respiratory distress syndrome; SLE: Systemic lupus erythematosus; IgG: Immunoglobulin G; IgM: Immunoglobulin M; HRCT: High resolution CT; IHC: Immunohistochemistry; BAL: Bronchoalveolar lavage; HPE: Histopathological examination; EIA: Enzyme immune assay; PCR: Polymerase chain reaction.

Immunohistochemistry (IHC) was reported in 24% of the cases, and biopsy-histopathology was performed in 27% of the patients. The treatment was reported in 84% of the cases, with a high recovery rate of 89%. Unfortunately, the mortality rate was 9%, with four patients reported to have died.

DISCUSSION

This paper analyzed 45 cases of CMV-induced pneumonia. Patients were divided into two main categories: Immunocompetent and immunocompromised. Twenty-nine (64%) patients were immunocompromised, and 16 (36%) were immunocompetent and developed CMV pneumonia. This suggests that CMV infection prevalence is higher in immunocompromised patients[2]. The reported case highlights the importance of considering CMV infection in patients who present with fever, respiratory symptoms, and abnormal liver function tests. Although CMV infection is more common in immunocompromised patients, this case demonstrates that it can also occur in immunocompetent individuals. It

Table 2 Baseline features of 45 patients with cytomegalovirus pneumonia

Variable	Patients, *n* = 45 (100%)
Age group	
0–15 yr	7 (15.6)
16–45 yr	25 (55.6)
46–75 yr	13 (28.8)
Sex	
Male	26 (58)
Female	19 (42)
Symptoms	
Fever	37 (82)
Cough	24 (53)
Dyspnoea	34 (76)
Resp. distress	26 (58)
Immune status	
Immunocompetent	16 (36)
Immunocompromised	29 (64)
Radiograhic findings	
Chest X-ray	32 (71)
Thoracic CT	31 (69)
Serology	
Blood/serum	40 (89)
Bronchoalveolar fluid (BAL)	18 (45)
Specific tests	
Immunohistochemistry	11 (24)
Biopsy - histopathology	12 (27)
Treatment	38 (84)
Recovery	40 (89)
Died	4 (9)

Table 3 Summary of data collected

	Immunocompetent	Immunocompromised
Total	16	29
Fever	13	24
Cough	11	13
Dyspnoea	12	22
Respiratory distress	10	16
Treatment	12	26
Recovered	15 (94%)	25 (86%)

is important to note that CMV is a common cause of pneumonia, particularly in immunocompromised patients, and should be considered in the differential diagnosis of patients with respiratory symptoms who do not respond to standard treatment. Early diagnosis and treatment are essential in improving patient outcomes, especially in severe cases. Therefore, clinicians should be aware of the clinical features

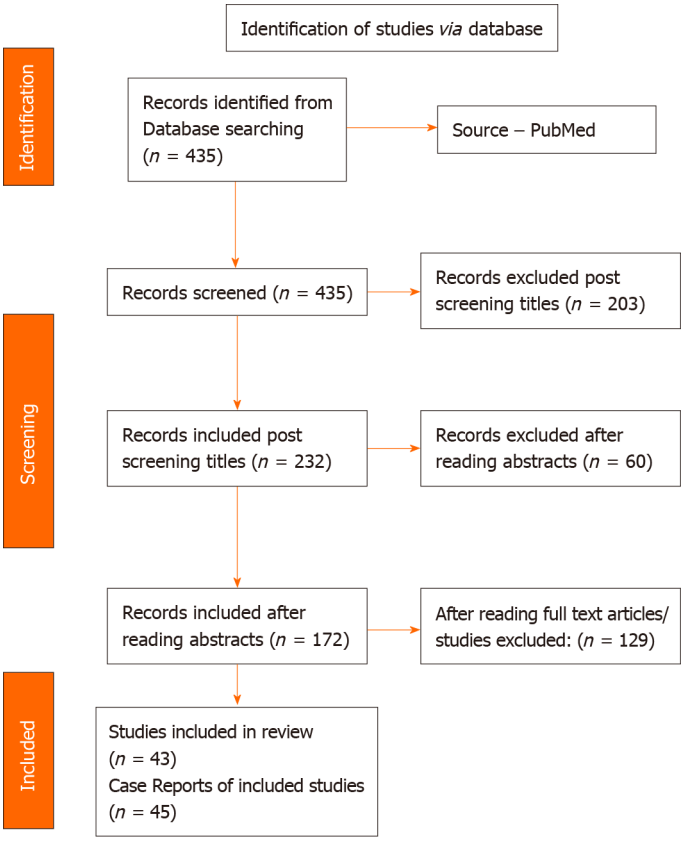

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Figure 2 PRISMA search strategy for systematic review.

and radiological findings of CMV pneumonia to enable early diagnosis and appropriate management [17-20].

The differential diagnosis of this case includes severe COVID-19 infection, which shares some clinical features with CMV pneumonia, such as cough, dyspnea, and fever. However, some features of the case, such as jaundice, hepatosplenomegaly, and pancytopenia, are not typically seen in severe COVID-19 cases. Additionally, GGOs on CT imaging can be seen in both CMV pneumonia and COVID-19. Therefore, it is important to consider other infectious and non-infectious etiologies in patients with respiratory symptoms and abnormal liver function tests.

A systematic review was performed a total of 45 patients, of which 26 (58%) were male and 19 (42%) were female. Infection was more prevalent in males, with 11 immunocompetent and 15 immunocompromised male patients and 5 immunocompetent and 14 immunocompromised female patients. This suggests that CMV infection is more prevalent in immunosuppressed patients in both males and females. Immunocompromised states are an important host-associated risk factor to get CMV infection [2].

Regarding age, 25 patients were adults (13 males and 12 females), indicating that the adult population is more prone to developing pulmonary CMV infection. As it is estimated that more than half of the adult population are infected with CMV in the United States, and 80% of the adult population have this infection by the age of 40 years, the prevalence of CMV-induced pneumonia may increase with age[1]. The clinical findings of most patients were fever (82%), dyspnea (75%), cough (53%), and respiratory distress (53%) in both immunocompetent and immunocompromised patients. These findings are consistent with previous studies on CMV pneumonia[4].

Regarding radiological findings, 32 patients were submitted to a chest X-ray mostly showing bilateral diffuse pulmonary infiltrates. CT of the thorax was done in 31 patients, and the main finding was bilateral GGOs. In some patients, there were small bilateral pulmonary nodules, confluent consolidations, and bronchiectasis. In case of atypical radiological findings other than bilateral infiltrates and GGOs, further investigation, such as blood and BAL serology, lung biopsy histopathological examination (HPE), and IHC, should be considered to rule out CMV pneumonia[7].

Blood serology was done in 40 (89%) patients, and IgM and IgG were positive for CMV. Other tests, such as BAL fluid serology, lung biopsy histopathology, and IHC, were done to confirm the diagnosis in some patients. IgM CMV positive in blood represents acute CMV infection, and antiviral treatment was given to the patients with a successful outcome[2,5].

A study by Basinger *et al*[24] demonstrated that immunocompromised states, particularly those with a history of allogenic hematopoietic stem cell transplant, can result in rapidly deteriorating conditions and respiratory status post-CMV infection. Radiologically, patients may present with rapidly progressive bilateral pulmonary nodules approximately 2 mo after receiving a bone marrow transplant. This patient died shortly after admission, and the diagnosis was made on post-mortem microscopic examination of the pulmonary nodules that demonstrated viral cytopathologic changes consistent with CMV infection, confirmed by IHC. It is essential to note that the radiographic presentation is not always GGOs, and rapidly enlarging pulmonary nodules in an immunosuppressed patient are highly suggestive of an infectious process. Therefore, careful histologic examination for viral cytopathologic changes is essential[3].

Regarding treatment, 38 (85%) patients received antiviral therapy, and 2 patients recovered without receiving antiviral treatment. In total, 89% of patients recovered, indicating that the prognosis of CMV pneumonia is good if diagnosed early and treated in time, in both immunocompetent and immunocompromised patients[2]. A study by Al-Eyadhy *et al*[32] in 2017 presented the case of a 12-year-old immunocompetent patient who was admitted with severe ARDS and developed multi-organ failure, which is an important differential diagnosis from severe acute respiratory syndrome coronavirus 2 infection. Due to the correct diagnosis and treatment of CMV infection in time, the patient recovered. Another study by Coussement *et al*[42] in 2016 showed that a 63-year-old immunocompromised patient who did a bilateral lung transplant for chronic obstructive pulmonary disease admitted with severe CMV infection and due to timely diagnosis and antiviral treatment, the patient recovered well.

In immunocompetent patients, the recovery rate was 94%, while in immunocompromised patients, it was 86%. The study showed that there were four deaths, three of which were among immunocompromised patients. This suggests that immunocompromised patients may develop more severe CMV illness that deteriorates quickly, sometimes making it challenging to make a timely diagnosis. Therefore, it is crucial to consider CMV infection as one of the important differentials in immunocompromised patients[1,4].

The final result of this analysis showed that 89% of total patients recovered, indicating that the prognosis of CMV pneumonia is good if patients are diagnosed early and treated promptly, even for immunocompromised patients[1,4].

To reach a definitive diagnosis, clinical findings must be correlated with imaging tests and laboratory tests. Polymerase chain reaction (PCR) is the most sensitive method of detecting CMV, and qRT-PCR can be used to quantify viral loads in blood and BAL fluid. BAL CMV-PCR is considered the most accepted approach for viral isolation in the lungs due to its high sensitivity. Lung biopsy histopathology is considered the gold standard for the diagnosis of pulmonary CMV infections, and the presence of CMV inclusions in the HPE report is confirmatory of lung infection. Additionally, CMV can be detected by IHC staining for CMV in cytologic specimens of bronchial lavage fluid[1,2].

In critically ill patients, CMV infection is associated with prolonged mechanical ventilation, nosocomial infections, prolonged hospital and ICU stay, and increased mortality. The first-line treatment for CMV disease is intravenous ganciclovir and its prodrug, oral valganciclovir. Mild disease in immunosuppressed patients may be treated with oral valganciclovir, while severe illness is treated with IV ganciclovir or foscarnet at full doses (adjusted for renal function), followed by valganciclovir. Treatment at full doses should be continued until the resolution of symptoms and blood antigenemia (or DNAemia) is cleared. The prognosis of CMV pneumonia is good if patients are diagnosed and treated at an early stage[1,2,4]. This systematic review aimed to understand the pattern, presentations, clinical course, and outcome of patients with COVID-19 and CMV coinfection and analyzed data from 34 reports with 59 patients. The results showed that middle-aged and elderly patients with comorbidities were more susceptible to coinfection, and CMV colitis was the most common manifestation of end-organ involvement. The findings of this study may assist in detecting and treating patients with unusual clinical courses or severe, prolonged, or unexplained deterioration of end-organ function[64].

CONCLUSION

In conclusion, CMV pneumonia is a serious complication in both immunocompromised and immunocompetent patients, with a higher morbidity and mortality rate in the former group. The diagnosis of CMV pneumonia can be challenging as it may present with nonspecific clinical and radiological features similar to COVID-19 pneumonia. Therefore, it is crucial to consider CMV infection as a differential diagnosis in immunocompromised patients with respiratory symptoms. Early diagnosis and treatment with antiviral therapy can lead to a good prognosis, while delayed diagnosis and treatment can lead to a more severe illness and potentially fatal outcomes. Clinicians should have a high index of suspicion for CMV pneumonia in immunocompromised patients and perform appropriate diagnostic tests, such as PCR and histopathological examination. Further research is needed to better understand the pathogenesis, risk factors, and optimal management of CMV pneumonia.

ARTICLE HIGHLIGHTS

Research background

Cytomegalovirus (CMV) is a DNA virus that can cause severe disease in immunocompromised patients and is common in recipients of hematopoietic stem cell transplantation. CMV is acquired through direct contact with infected cells or body fluids, and transmission can occur from a CMV-seropositive donor organ. Congenital CMV, transmitted from infected mothers to their newborns, is a leading cause of miscarriage. CMV is one of the three most common causes of severe viral community-acquired pneumonia, but this has changed with the emergence of severe acute respiratory syndrome coronavirus 2 in 2020.

Research motivation

During the COVID-19 pandemic, it is important to differentiate clinical and radiological presentations from other diseases. Ground-glass opacities (GGOs) require evaluation along with other tests to reach a diagnosis. To diagnose CMV pneumonia, the virus can be detected in serum or respiratory samples, and quantitative real-time PCR can measure viral loads in blood and BAL fluid. Lung biopsy histopathology is the gold standard for diagnosing pulmonary CMV infections. However, the diagnostic yield of lung biopsy varies, and the study of CMV pneumonia in immunocompetent patients with GGOs remains limited.

Research objectives

This study aimed to report a case of CMV pneumonia in an immunocompetent patient with GGOs on chest CT, to review the literature on the clinical, radiological, and laboratory features of CMV pneumonia in immunocompetent hosts, and to discuss the diagnostic workup and management of CMV pneumonia.

Research methods

This study followed PRISMA guidelines to identify case reports and case series studies on pulmonary complications of CMV infection. The selection criteria included studies that reported only CMV pneumonia without other co-existing causes of pneumonia. Data extraction involved identifying the characteristics of the subjects and the outcomes measured. The patient case report presented in the article was included in the study as it met the inclusion criteria, and the patient received ganciclovir therapy resulting in complete recovery from symptoms and sustained undetectable viral load after 6 wk of treatment.

Research results

The study found 45 case reports of pulmonary CMV infection after analyzing 435 references. The majority of the patients were males (58%) in the age group of 16-45 years (55.6%). Common symptoms included fever, dyspnea, and cough, with respiratory distress observed in 58% of the cases. Most patients (64%) were immunocompromised. Radiographic findings were reported in 71% of the patients, and blood/serum was the most commonly used method for diagnosis. Treatment was reported in 84% of the cases, with a high recovery rate of 89%, but the mortality rate was 9%. Early diagnosis and prompt treatment are crucial to improve outcomes and reduce mortality rates, especially in immunocompromised individuals.

Research conclusions

The study analyzed 45 cases of CMV-induced pneumonia and found that it can occur in both immunocompetent and immunocompromised patients, with clinical findings of fever, dyspnea, cough, and respiratory distress. Radiological findings showed bilateral diffuse pulmonary infiltrates and bilateral GGOs. Blood serology was positive for CMV, and antiviral treatment was given with a successful outcome. The recovery rate was high, but four deaths were reported, with three among immunocompromised patients.

Research perspectives

Future studies can investigate the prevalence of CMV pneumonia in different age groups and genders, and the possible link between CMV and COVID-19. The effectiveness of antiviral therapy in preventing severe CMV illness and the optimal duration of treatment can be evaluated. Pathophysiology and immunology of CMV pneumonia in immunocompromised patients need further research.

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FOOTNOTES

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SYSTEMATIC REVIEWS

Real-world effectiveness of mRNA COVID-19 vaccines in the elderly during the Delta and Omicron variants: Systematic review

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Abstract

BACKGROUND

As of 31 December 2022, there were over 6.6 million coronavirus disease 2019 (COVID-19) deaths and over 651 million cases across 200 countries worldwide. Despite the increase in vaccinations and booster shots, COVID-19 cases and deaths continue to remain high. While the effectiveness of these vaccines has already been established by different manufacturers, the fact remains that these vaccines were created quickly for global emergency use, tested under controlled clinical conditions from voluntary subjects and age groups whose general characteristics may differ from the actual general population.

AIM

To conduct a systematic review to determine the real-world effectiveness of mRNA COVID-19 vaccines in the elderly during the predominance of Delta and Omicron variants in preventing COVID-19 related infection, hospital, intensive care unit (ICU) admission and intubation, and death.

METHODS

A combination of Medical Subject Headings and non–Medical Subject Headings was carried out to identify all relevant research articles that meets the inclusion and exclusion criteria from PubMed, Cochrane, CINAHL, Scopus, ProQuest, EMBASE, Web of Science, and Google Scholar databases, as well as qualified research studies from pre–print servers using medRxiv and Research Square, published from January 1, 2021 - December 31, 2022.

RESULTS

As per the inclusion and exclusion criteria, the effectiveness of Pfizer-BioNTech and Moderna vaccines were evaluated from an estimated total study population of 26535692 using infection, hospital, ICU admission and intubation, and death as outcome measures from studies published between 2021 and 2022, conducted in New York, Finland, Canada, Costa Rica, Qatar, Greece, and Brazil. The risk of bias was evaluated using risk of bias in nonrandomized studies of interventions

(ROBINS-I) tool for cohort, case-control, and cross-sectional studies. While clinical trial data on Pfizer-BioNTech and Moderna vaccines demonstrated 94% vaccine effectiveness in the elderly, the results in this study showed that vaccine effectiveness in real-world settings is marginally lower against infection (40%-89%), hospitalization (92%), ICU admission and intubation (98%-85%), and death (77%-87%) with an indication of diminished effectiveness of vaccine over time. Furthermore, 2 doses of mRNA vaccines are inadequate and only provides interim protection.

CONCLUSION

Because of the natural diminishing effectiveness of the vaccine, the need for booster dose to restore its efficacy is vital. From a research perspective, the use of highly heterogeneous outcome measures inhibits the comparison, contrast, and integration of the results which makes data pooling across different studies problematic. While pharmaceutical intervention like vaccination is important to fight an epidemic, utilizing common outcome measurements or carrying out studies with minimal heterogeneity in outcome measurements, is equally crucial to better understand and respond to an international health crisis.

Key Words: COVID-19; mRNA Vaccine; Effectiveness; Elderly; Delta; Omicron; Systematic review

Core Tip: This systematic review investigates the real-world effectiveness of mRNA coronavirus disease 2019 (COVID-19) vaccines in reducing morbidity and mortality in the elderly during the predominance of Delta and Omicron variants. This study found that the effectiveness of mRNA COVID-19 vaccines in the elderly against the Delta and Omicron variants is marginally lower than what was suggested in clinical trial data. Vaccine efficacy also diminishes over time, indicating the need for a booster dose to restore its effectiveness. Furthermore, to better understand and respond to an epidemic, studies should utilize common outcome measurements or minimize heterogeneity in outcome measures to facilitate data comparison and integration of results.

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INTRODUCTION

As of December 31, 2022, there were over 6.6 million coronavirus disease 2019 (COVID-19) deaths and over 651 million cases across 200 countries worldwide[1]. During the second half of 2021, COVID-19 cases and deaths were predominantly influenced by the Delta and Omicron variants, wreaking havoc even in countries with tough COVID-19 restrictions[2,3]. Epidemiological studies have shown that the contagious and highly transmissible nature of the Delta and Omicron variants has even put the elderly population in a more disadvantaged position, accounting roughly 14% of all COVID-19 cases and 70% of all COVID-19 deaths as of December 31, 2022[4-7]. While there is no broad consensus on the age at which a person can be considered elderly, the approved cutoff age as per the United Nations is 60+ years[8].

As a response to the extensive impact of COVID-19, which has become a public health concern and an international health crisis, the Centers for Disease Control and Prevention rolled out a global strategy response framework which outlined a combination of non-pharmaceutical and pharmaceutical interventions[9-11]. While the primary method of epidemic control has been non-pharmaceutical measures, pharmaceutical intervention, like vaccine, is expected to be the only effective, long-term defense against infection and death[12,13]. Vaccination is critical since the epidemic is still challenging to control due to the dormant symptoms and contagious nature of the virus especially during the incubation period which triggers late detection of infection[12,13].

Of the 356 vaccine candidates, over 12 billion vaccine doses have been administered by 34 different vaccines approved under Emergency Use Authorization[1,14]. Despite the increase in vaccinations and booster shots, COVID-19 cases and deaths continue to remain high[1]. While the effectiveness of these vaccines has already been established by different manufacturers, the fact remains that these vaccines were created quickly for global emergency use, tested under controlled clinical conditions from voluntary subjects and age groups whose general characteristics may differ from the actual general

population[15-17]. In spite of the many observational studies providing data on the effectiveness of vaccination in various populations, this study aims to compile the disparate data through systematic review[18-29]. This study carefully examines the effectiveness of COVID-19 vaccines in real-world settings in the elderly during the predominance of Delta and Omicron variants.

MATERIALS AND METHODS

The systematic review was designed according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) standards to ensure a comprehensive and methodical approach[30].

Search strategy and selection criteria

The review searched for qualified studies using a combination of Medical Subject Headings (MeSH) and non–Medical Subject Headings from PubMed, Cochrane, CINAHL, Scopus, ProQuest, EMBASE, Web of Science, and Google Scholar databases, as well as qualified research studies from pre–print servers using medRxiv and Research Square, published from January 1, 2021 – December 31, 2022. The search was independently performed by a single researcher using the following keywords and search terms (Supplementary Table 1: Keywords and Search Terms using PICO): (1) Covid-19; covid 19; covid19; SARS CoV 2*; SARS-CoV-2*; SARS Coronavirus 2 Infection; sars virus; 2019 Novel Coronavirus*; nCoV; 2019-nCoV*; COVID-19 Pandemic*; COVID-19 Virus*; Coronavirus; Coronavirus Disease*; Severe Acute Respiratory Syndrome Coronavirus 2 Infection; CV-19; CV19; (2) covid 19 vaccine*; covid-19 vaccine*; Pfizer-BioNTech vaccine; Comirnaty; BNT162b2; Bnt-162b2; Bnt162b2; Tozinameran; Tozinameran [INN]; UNII-5085ZFP6SJ; Moderna vaccine; mRNA-1273; MRNA-1273; Spikevax; CX-024414; Elasomeran; Elasomeran [INN]; M-1273; Moderna covid-19 vaccine rna; TAK-919; UNII-EPK39PL4R4; Covid 19 booster; Covid-19 booster; SARS-CoV-2 vaccine; SARS-CoV-2 booster; vaccinated; inoculat*; immuni*; post-vaccination; antibody; protected; (3) unvaccinated; uninoculated; uninoculated; unimmunized; unprotected; susceptible; and (4) reduce incidence*; reduce admission*; reduce infection*; reduce hospitalization*; reduce morbidity*; reduce mortality*; reduce death*; lessen infection*; lessen admission*; lessen hospitalization*; lessen morbidity*; lessen mortality*; lessen death *; prevent incidence*; prevent infection*; prevent admission*; prevent hospitalization*; prevent morbidity*; prevent mortality*; prevent death*; minimize incidence*; minimize admission*; minimize infection*; minimize hospitalization*; minimize morbidity*; minimize mortality*; minimize death*; control incidence*; control admission*; control infection*; control hospitalization*; control morbidity*; control mortality*; control death*; combat incidence*; combat admission*; combat infection*; combat hospitalization*; combat morbidity*; combat mortality*; combat death*; eliminate incidence*; eliminate admission*; eliminate infection*; eliminate hospitalization*; eliminate morbidity*; eliminate mortality*; eliminate death*; diminish incidence*; diminish admission*; diminish infection*; diminish hospitalization*; diminish morbidity*; diminish mortality*; diminish death*; solve incidence*; solve admission* ; solve infection*; solve hospitalization*; solve morbidity*; solve mortality*; solve death*.

Eligibility standards: inclusion and exclusion criteria

In accordance to the inclusion criteria, the systematic review identified relevant English-published observational studies, which examined the effectiveness of COVID-19 vaccines among the: (1) Elderly populations who were ≥ 60 years old; (2) recipient of at least 2 doses of mRNA (Pfizer-BioNTech and Moderna) vaccines; (3) during the predominance of Delta (B.1.617.2) or Omicron (B.1.1.529/BA); and (4) studies which examined subjects as COVID-19 positive based on a positive Reverse Transcription Polymerase Chain Reaction (RT-PCR or PCR) tests as well as studies which compared and examined the incidence of COVID-19, infection, hospitalization, admission to intensive care unit (ICU), intubation, and death. This systematic review, however, will not include: (1) Systematic review and meta-analysis studies, case reports, case series, reviews, editorials, conference papers, letters, and correspondence; (2) studies on animals; (3) studies with mathematical modelling analysis; (4) studies with insufficient data to calculate the prevention rate of COVID-19; (5) studies with immunocompromised subjects; (6) studies which did not have an unvaccinated subjects to compare; (7) studies that did not use SARS-CoV-2 vaccination as the exposure; (8) duplicate studies or studies with overlapping participants; and (9) studies that did not explain how COVID-19 subjects were determined (Figure 1).

Data extraction and outcomes

The review process underwent 4 stages: (1) All the papers found within the identified databases were examined and the publication year, study titles, authors, and abstracts were imported into an Excel spreadsheet; (2) the records were managed, screened and duplicates were eliminated manually by assessing the study title, authors, and abstract for inclusion; (3) only those with titles and abstracts that match the inclusion criteria were retrieved and carefully evaluated for full text review; and (4) using a separate Excel spreadsheet, a data extraction sheet was developed to independently extract the general study characteristics (author and publication year, study design, location, purpose, study population,

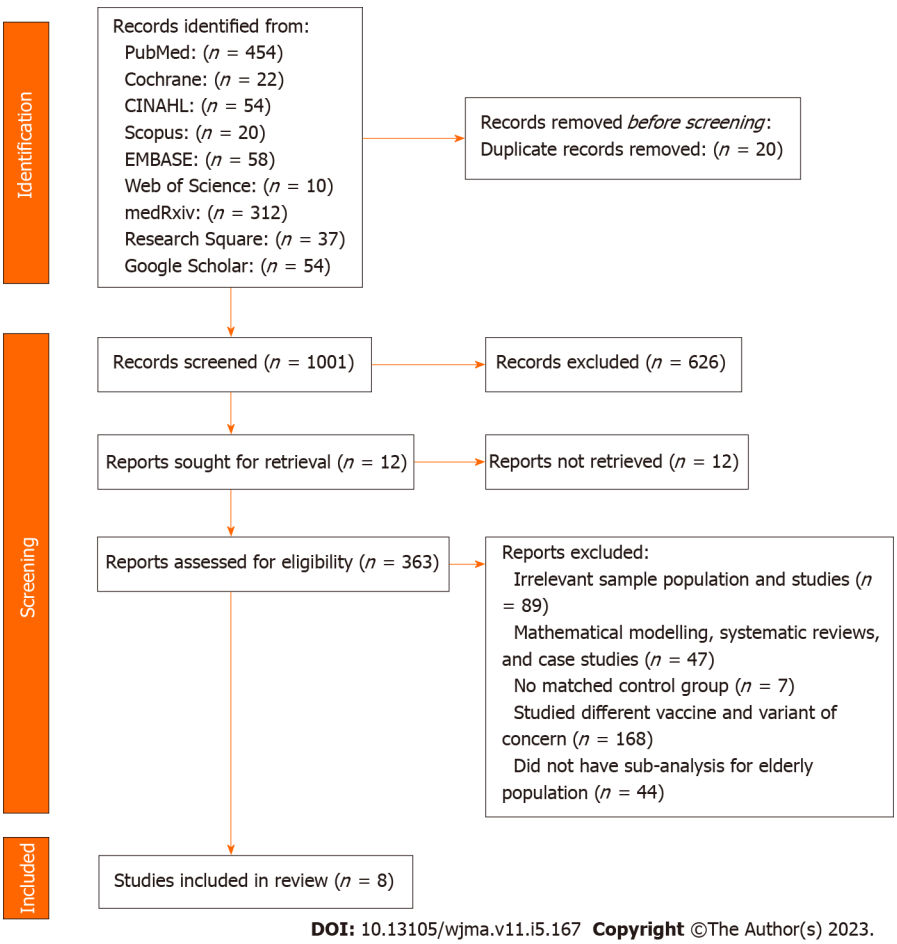

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Figure 1 Flow diagram of study identification and selection process.

including age of study population, variant of concern, vaccine type, number of doses received, outcome measures, vaccine effectiveness, and results). All qualified studies for systematic reviews were imported, stored, and managed in EndNote20.

The studies included in the review were assessed based on: (1) Age of study population; (2) variant of concern; (3) type of vaccine used; and (4) effectiveness of vaccines based on outcome measures. The effectiveness of COVID-19 mRNA vaccines in reducing morbidity and mortality were examined by comparing the following outcomes amongst the selected studies:

(1) Effectiveness of COVID-19 mRNA vaccines to reduce morbidity in terms of infections, hospitalization, admission to ICU and intubation;

And (2) effectiveness of COVID-19 mRNA vaccines to reduce mortality or deaths.

This study did not require the approval of an ethical committee or an Institutional Review Board since data collection and synthesis were gathered from already published studies in which proper consent or approvals would have been obtained by the researchers.

Quality assessment and data synthesis

The methodological quality of these observational studies was assessed through the risk of bias using ROBINS-I tool (risk of bias in non-randomized studies of interventions) and were analyzed using a narrative synthesis method which gathered the information from several sources and employed words and text to summarize and explain the findings since meta-analysis is not practical due to significant heterogeneity between the studies[31,32].

RESULTS

Study selection process and study characteristics

After searching 9 different databases, 1,021 studies were identified from PubMed (n = 454), Cochrane (n = 22), CINAHL (n = 54), Scopus (n = 20), EMBASE (n = 58), Web of Science (n = 10), medRxiv (n = 312), Research Square (n = 37), and Google Scholar (n = 54). From the preliminary review, 20 duplicates, 626 unrelated, and 12 unretrieved studies were excluded, leaving 363 studies were moved for title and

Table 1 Characteristic of studies included for vaccine effectiveness

Ref.	Study design	Location	Purpose	Age of study group	Vaccine type	Number of doses received	Variant of concern
Baum *et al*[33], 2022	Cohort study	Finland	To estimate VE against severe COVID-19 among the elderly	Adult population including ≥ 70 yr old	Pfizer-BioNTech	2 doses	Omicron
Grewal *et al* [34], 2022	Case control design	Canada	To estimate vaccine effectiveness of mRNA vaccines among aged ≥ 60 yr who were tested for SARS-CoV-2	≥ 60 yr old	Pfizer-BioNTech and Moderna	Booster	Omicron
Rosenberg *et al* [35], 2021	Cohort study	USA (NY)	To describe vaccine efficacy in NY	Adult population including ≥ 50 yr old	Pfizer-BioNTech and Moderna	2 doses	Delta
Rosero-Bixby [36], 2021	Cross-sectional study	Costa Rica	To estimate the dose-dependent effectiveness of coronavirus disease (COVID-19) vaccines to prevent severe illness in real-world conditions	Adult population including ≥ 58 yr old	Pfizer-BioNTech	2 doses	Delta
Rane *et al*[37], 2022	Case control study	USA (NY)	To monitor changes in vaccine effectiveness against COVID-19 outcomes for various vaccine products in different population subgroups	Adult population including ≥ 50 yr old	Pfizer-BioNTech	2 doses	Delta
Chemaitelly *et al*[38], 2021	Case control study	Qatar	To estimate vaccine effectiveness against any SARS-CoV-2 infection and against any severe, critical, or fatal case of COVID-19	Adult population including ≥ 50 yr old	Pfizer-BioNTech	2 doses	Delta
Lytras *et al* [39], 2022	Cohort study	Greece	To estimate COVID-19 effectiveness against disease and death	Adult population including ≥ 60 yr old	Pfizer-BioNTech and Moderna	2 doses and booster	Delta
Ranzani *et al* [40], 2022	Case control study	Brazil	To evaluate vaccine effectiveness against symptomatic COVID-19 and severe COVID-19 (hospital admission or deaths)	Adult population including ≥ 70 yr old	Pfizer-BioNTech	2 doses and booster	Omicron

COVID-19: Coronavirus disease 2019; SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2; USA (NY): United States of America (New York); VE: Vaccine effectiveness.

abstract screening. As per the inclusion and exclusion conditions in the eligibility criteria, 354 studies were excluded for the following reasons: (1) Irrelevant sample population and studies (n = 89); (2) mathematical modelling, systematic reviews, and case studies (n = 47); (3) no matched control group (n = 7); (4) studied different vaccine and variant of concern (n = 168); (4) did not have sub-analysis for elderly population (n = 43); and (5) overlap in study population (n = 1). As a result, only 8 studies were included for systematic review[33-40]. PRISMA Flow Diagram summarized the literature selection process (Figure 1).

Among these studies, 3 were published and 5 were published on the pre-print platforms[33-40]. All of the 8 studies used observational study designs such as cohort, case control, and cross-sectional studies [33-40]. These studies reported the effectiveness of Pfizer-BioNTech (n = 8) and Moderna (n = 4) vaccines, with 7 studies examining 2 doses, 2 studies examining 2nd and booster doses, and 1 study examining booster dose in reducing COVID-19 morbidity and mortality during the prevalence of Delta (B.1.617.2) and Omicron (B.1.1.529/BA) variants[33-40]. Study locations were in New York, Finland, Canada, Costa Rica, Qatar, Greece, and Brazil published between 2021 (n = 3) and 2022 (n = 5)[33-40]. The studies compared an estimated total sample size of 8740562 vaccinated elderly people and 9658245 unvaccinated elderly cohorts from an estimated total study population of 26535692 which evaluated the effectiveness of mRNA vaccines of an adult population including elderly cohorts who were 50 years old and older[33-40]. Although the goal of the study is to focus on elderly subjects who were 60 years old and older, some of the selected studies in this review, grouped the elderly subjects from 50 years old to include 60 years old and older subjects[35-38]. The largest sample size of vaccinated elderly people was 3479102 and 8138482 unvaccinated elderly cohorts while the smallest sample size of vaccinated and unvaccinated elderly people was 45345 and 1272, respectively[34,35,39]. The outcome measures used by the selected studies defined morbidity as infection (n = 5), hospitalization (n = 6), admission to ICU and intubation (n = 2) and mortality or death (n = 4) as outcome measurements[33-40]. The characteristics of included studies are shown in Tables 1 and 2.

Risk of bias

The risk of bias was evaluated by following ROBINS-I tool (risk of bias in non-randomized studies of interventions)[31]. All of the 8 observational studies were rated to have moderate risk of bias mainly

Table 2 Characteristic of participants included for vaccine effectiveness

Ref.		Age of study population	mRNA vaccinated elderly participants with 2 doses	mRNA vaccinated participants with 2 doses according to vaccine type		mRNA vaccinated elderly participants with 2 doses according to age		Unvaccinated elderly participants	Unvaccinated elderly participants according to age
				Pfizer-BioNTech	Moderna	Pfizer-BioNTech	Moderna		
Baum *et al* [33], 2022	897932	Adult population including ≥ 70 yr old	241630	-	-	70-79 yr old: 171816; 80-89 yr old: 57024; 90-115 yr old: 12790		747486	70-79 yr old: 480532; 80-89 yr old: 223267; 90-115 yr old: 43687
Grewal *et al* [34], 2022	46849	≥ 60 yr old	45345	-	-	-	-	1272	-
Rosenberg *et al*[35], 2021	8834604	Adult population including ≥ 50 yr old	3479102	-	-	50-64 yr old: 846664; ≥ 65 yr old: 984464	50-64 yr old: 624226; ≥ 65 yr old: 1023748	976536	50-64 yr old: 606411; ≥ 65 yr old: 370125
Rosero-Bixby[36], 2021	3670000	Adult population including ≥ 58 yr old	741474	-	-	741474		58887	58887
Rane *et al* [37], 2022	1058493	Adult population including ≥ 50 yr old	143104	-	-	50-59 yr old: 64806; 60-69 yr old: 48260; 70-79 yr old: 22997; ≥ 80 yr old: 7041		27362	50-59 yr old: 14936; 60-69 yr old: 8352; 70-79 yr old: 3066; ≥ 80 yr old: 1008
Chemaitelly *et al*[38], 2021	-	Adult population including ≥ 50 yr old	1402622	907763	494859	-	-	8043	50-59 yr old: 6350; 60-69 yr old: 1326; ≥ 70 yr old: 367
Lytras *et al* [39], 2022	9200000	Adult population including ≥ 60 yr old	2380402	2128913	251492	-		-	8138482
Ranzani *et al* [40], 2022	1417149	Adult population including ≥ 60 yr old	306883	-	-	60-79 yr old: 258306; ≥ 80 yr old: 48577		306588	60-79 yr old: 265073; ≥ 80 yr old: 41515

due to lack of control for confounders such as comorbidities or socioeconomic status like age and occupation, outbreak data such as location and time of test, and other risk-taking behavior modification [33-40]. Due to the dependence in surveillance data which were subject to incomplete information, 5 studies received a moderate risk of bias score because of missing data, while 3 studies due to misclassification of measurement of outcomes, were rated with moderate bias[35-40]. Table 3 shows the results of ROBINS-I risk of bias assessment of observational studies.

Synthesis of results

Vaccine effectiveness against infection: 5 of the 8 studies (36%) reported the effectiveness of vaccines using infection as an outcome measure[34,35,37,38,40]. Among these, 2 of the studies used booster dose to evaluate vaccine effectiveness against asymptomatic and symptomatic infections while 3 studies assessed the effectiveness of 2 doses of vaccines[34,35,37,38,40]. The findings from these studies revealed that 2 doses of mRNA vaccines offer 83%-89% protection against infection, while other studies revealed vaccine's protection level against infection at 40%-63%, marginally lower for 65 years old when compared to Moderna, Pfizer-BioNTech vaccine was reported to have slightly lower efficacy against infections with indications of declining protection over a period of time[34,35,37,38,40].

Vaccine effectiveness against hospitalization: 3 of the 8 studies (21%) reported the effectiveness of vaccines using hospitalization as an outcome measure which demonstrated 92% efficacy for older people[33,35,36]. Similarly, when compared to Moderna, Pfizer-BioNTech vaccine have lower marginal protection against hospitalization with indication of waning effectiveness against hospitalization, 6 months after the 2nd dose[33,35].

Vaccine effectiveness against ICU admission and intubation: 2 out of the 8 studies (14%) reported the effectiveness of vaccines using admission to ICU and intubation as outcome measures[33,39]. The study on ICU admissions revealed that Pfizer-BioNTech vaccine's protection waned from 98% down to 85%

Table 3 ROBINS-I risk of bias assessment of observational studies

Ref.	Confounding	Selection of participants	Classification of interventions	Deviations from interventions	Missing data	Measurement of outcomes	Reported result	Overall bias
Baum *et al* [33], 2022	Moderate	Low	Moderate	Moderate	Low	Low	Low	Moderate
Grewal *et al* [34], 2022	Moderate	Moderate	Low	Low	Low	Low	Low	Moderate
Rosenberg *et al* [35], 2021	Moderate	Moderate	Low	Low	Moderate	Low	Low	Moderate
Rosero-Bixby [36], 2021	Moderate	Low	Low	Low	Moderate	Moderate	Low	Moderate
Rane *et al*[37], 2022	Low	Low	Low	Low	Moderate	Low	Low	Low
Chemaitelly *et al*[38], 2021	Moderate	Low	Low	Low	Moderate	Low	Low	Moderate
Lytras *et al* [39], 2022	Moderate	Low	Low	Low	Moderate	Moderate	Low	Moderate
Ranzani *et al* [40], 2022	Low	Low	Low	Low	Low	Moderate	Low	Moderate

Low risk: Comparable to a well-performed randomised trial; Moderate risk: Sound for a non-randomised study but cannot be compared to a well performed randomised trial; Serious risk: Study has some important problems; Critical risk: Study is too problematic to provide any useful evidence.

after 6 months among 70 years old and older[33]. Similar findings was observed when intubation was used as an outcome measure, which revealed diminished vaccine effectiveness from 96.9% down to 86%, in 6 months among 60 years old and older populations but was restored at 97.6% by booster dose [39].

Vaccine effectiveness against death: 4 out of the 8 studies (29%) reported the effectiveness of vaccines using death with hospitalization as outcome measures[34,38-40]. The findings showed that although 2 doses of mRNA vaccine can prevent death, it offers a marginally limited protection against death among 75 years old and older with indications of diminishing protection which was only restored by a booster dose[38-40]. Additionally, the finding showed that Pfizer-BioNTech has marginally higher protection level against death at 87% when compared to Moderna at 77%[34]. The outcomes of included studies for vaccine effectiveness are shown in Table 4.

DISCUSSION

While clinical trial data on Pfizer-BioNTech and Moderna vaccines demonstrated 94% effectiveness among the elderly, the results in this study showed that the effectiveness of mRNA vaccines in real-world settings is marginally lower against COVID-19 infection, hospitalization, ICU admission and intubation, and deaths during the predominance of Delta and Omicron variants[33-40].

The results in this systematic review further strengthen and supplement the increasing evidence on the real-world effectiveness of mRNA vaccines. While the inclusion and exclusion criteria of this review limits a variety of similar studies in the data analysis, for discussion purposes these studies echoed similar findings. A study conducted in United Kingdom revealed that vaccine effectiveness for ≥ 60 years old is 42.3%[41]. The same observed pattern is reported for ≥ 75 years old in a study conducted in Israel, in a case-control study conducted among US military personnel and in a test-negative design study conducted in Malaysia[42-44]. Using random-effects model on 15 observational studies to estimate the pooled vaccine effectiveness (VE) with 95% confidence intervals for each vaccine type against each variant, the systematic review and meta-analysis conducted by Zhang *et al*[45] revealed a limited vaccine effectiveness among ≥ 65 years old. The result in this study also align with the result in our study and with the findings of other studies focusing on vaccine effectiveness in the elderly during the predominance of Delta and Omicron variants[46-48]. Utilizing the same research model, a contrasting result was reported by Li *et al*[49] when they evaluated the effectiveness of vaccine in over 30000 participants aged 60 years and older. This systematic review and meta-analysis however, largely focused on randomized controlled trials which may have skewed the outcomes. Given that clinical trials on COVID-19 vaccines are conducted under controlled clinical conditions from volunteer subjects of targeted age groups, these studies are not able to take into account the abilities of COVID-19 to mutate

Table 4 Outcomes of studies included for vaccine effectiveness

Ref.	Outcome measurements					Vaccine effectiveness
	Infection (*n*/%)	Hospitalization (*n*/%)	ICU admission (*n*/%)	Intubation (*n*/%)	Death (*n*/%)	
Baum *et al* [33], 2022	-	2 doses of Pfizer (within 3 mo): 30/5.64%; 2 doses of Pfizer (within 6 mo): 193/36.28%; 2 doses of Pfizer (≥ 6 mo): 148/27.82%; 3 doses of Pfizer (within 3 mo): 95/17.86%; 3 doses of Pfizer (≥ 6 mo): 66/12.41%	2 doses of Pfizer (within 3 mo): 5/8.33%; 2 doses of Pfizer (within 6 mo): 24/40%; 2 doses of Pfizer (≥ 6 mo): 14/23.33%; 3 doses of Pfizer (within 3 mo): 9/15%; 3 doses of Pfizer (≥ 6 mo): 8/13.33%	-	-	Hospitalization: 2 doses of Pfizer (within 3 mo): 90%; 2 doses of Pfizer (within 6 mo): 85%; 2 doses of Pfizer (≥ 6 mo): 72%; 3 doses of Pfizer (within 3 mo): 95%; 3 doses of Pfizer (≥ 6 mo): 88%; ICU Admission: 2 doses of Pfizer (within 3 mo): 98%; 2 doses of Pfizer (within 6 mo): 95%; 2 doses of Pfizer (≥ 6 mo): 82%; 3 doses of Pfizer (within 3 mo): 98%; 3 doses of Pfizer (≥ 6 mo): 85%
Grewal *et al* [34], 2022	Infection: 3 doses of Pfizer: 2691/42.43%; 3 doses of Moderna: 3651/57.57%; Symptomatic Infection: 3 doses of Pfizer: 395/38.69%; 3 doses of Moderna: 626/61.31%	3 doses of Pfizer: 214/58.79%; 3 doses of Moderna: 150/41.21%	-	-	3 doses of Pfizer: 214/58.79%; 3 doses of Moderna: 150/41.21%	Infection: 3 doses of Pfizer: 31%; 3 doses of Moderna: 51%; Symptomatic Infection: 3 doses of Pfizer: 61%; 3 doses of Moderna: 73%; Hospitalization or Death: 3 doses of Pfizer: 87%; 3 doses of Moderna: 77%
Rosenberg *et al*[35], 2021	≥ 65 yr old (2 doses of Pfizer): 5302/61.70%; ≥ 65 yr old (2 doses of Moderna): 3291/38.30%	≥ 65 yr old (2 doses of Pfizer): 972/64.07%; ≥ 65 yr old (2 doses of Moderna): 545/35.93%	-	-	-	Infection: ≥ 65 yr old (2 doses of Pfizer): 83.0%; ≥ 65 yr old (2 doses of Moderna): 89.2%; Hospitalization: ≥ 65 yr old (2 doses of Pfizer): 91.9%; ≥ 65 yr old (2 doses of Moderna): 95.7%
Rosero-Bixby[36], 2021		40-57 yr old: 37/0.006%; ≥ 58 yr old: 65/0.009%	-	-	-	Hospitalization: 40-57 yr old: 94%; ≥ 58 yr old: 92%
Rane *et al* [37], 2022	60-69 yr old: 3232/5.8%; 70-79 yr old: 1221/2.2%; ≥ 80 yr old: 468/0.8%	-	-	-	-	Infection: 51-64 yr old: 60%; 65 80 yr old: 55%; ≥ 80 yr old: 51%
Chemaitelly *et al*[38], 2021	2 doses of Pfizer (within 1 mo): 2915/2.51%; 2 doses of Pfizer (within 2 mo): 1450/1.28%; 2 doses of Pfizer (within 3 mo): 800/0.71%; 2 doses of Pfizer (within 4 mo): 492/0.44%; 2 doses of Pfizer (within 5 mo): 548/0.49%; 2 doses of Pfizer (within 6 mo): 460/0.41%; 2 doses of Pfizer (≥ 7 mo): 135/0.12%	2 doses of Pfizer (within 1 mo): 32/0.78%; 2 doses of Pfizer (within 2 mo): 23/0.56%; 2 doses of Pfizer (within 3 mo): 17/0.42%; 2 doses of Pfizer (within 4 mo): 10/0.25%; 2 doses of Pfizer (within 5 mo): 0/0; 2 doses of Pfizer (within 6 mo): 8/0.20%; 2 doses of Pfizer (≥ 7 mo): 6/0.15%			2 doses of Pfizer (within 1 mo): 32/0.78%; 2 doses of Pfizer (within 2 mo): 23/0.56%; 2 doses of Pfizer (within 3 mo): 17/0.42%; 2 doses of Pfizer (within 4 mo): 10/0.25%; 2 doses of Pfizer (within 5 mo): 0/0; 2 doses of Pfizer (within 6 mo): 8/0.20%; 2 doses of Pfizer (≥ 7 mo): 6/0.15%	Infection: 2 doses of Pfizer (within 1 mo): 75.8%; 2 doses of Pfizer (within 2 mo): 69.7%; 2 doses of Pfizer (within 3 mo): 63.7%; 2 doses of Pfizer (within 4 mo): 39.1%; 2 doses of Pfizer (within 5 mo): 11.4%; 2 doses of Pfizer (within 6 mo): 9.2%; 2 doses of Pfizer (≥ 7 mo): -4.4%; Hospitalization and Death: 2 doses of Pfizer (within 1 mo): 95.9%; 2 doses of Pfizer (within 2 mo): 96.3%; 2 doses of Pfizer (within 3 mo): 93.4%; 2 doses of Pfizer (within 4 mo): 80.8%; 2 doses of Pfizer (within 5 mo): 100%; 2 doses of Pfizer (within 6 mo): 81.8%; 2 doses of Pfizer (≥ 7 mo): 44.1%
Lytras *et al* [39], 2022				2 doses of Pfizer: 548/90.28%; 2 doses of Moderna: 35/5.77%; 3 doses of Pfizer: 24/0.04%	2 doses of Pfizer: 1629/64.60%; 2 doses of Moderna: 42/2.44%; 3 doses of Pfizer: 51/5.96%	Intubation: 60-79 yr old (2 doses): 96.9%; ≥ 80 yr old (2 doses): 94.4%; ≥ 80 yr old (2 doses, within 6 mo): 86.0%; ≥ 80 yr old (3 doses): 97.6%; Death: 60-79 yr old (2 doses): 94.6%; ≥ 80 yr old (2 doses): 91.0%; ≥ 80 yr old (2 doses, within 6 mo): 84.1%; ≥ 80 yr old (3 doses): 98.4%
Ranzani *et al*[40], 2022	Symptomatic Infection: 60-74 yr old (2 doses): 34077/86.93%; ≥ 75 yr				60-74 yr old (2 doses): 2035/63.3%; ≥ 75 yr old (2 doses):	Infection: 60-74 yr old (2 doses): 63.4%; ≥ 75 yr old (2 doses): 40.7%; 60-74 yr old (3

	old (2 doses): 15539/79.84%; 60-74 yr old (3 doses, within 2 mo): 15053/64%; 60-74 yr old (3 doses, after 2 mo): 3273/66.36%; ≥ 75 yr old (3 doses, within 2 mo): 116955/89.86%; ≥ 75 yr old (3 doses, after 2 mo): 64495/99.36%	2750/52.81%; 60-74 yr old (3 doses, within 2 mo): 50/68.50%; 60-74 yr old (3 doses, after 2 mo): 51/96.01%; ≥ 75 yr old (3 doses, within 2 mo): 511/90.41%; ≥ 75 yr old (3 doses, after 2 mo): 2964/72.40%	doses, within 2 mo): 88.4%; 60-74 yr old (3 doses, after 2 mo): 90.4%; ≥ 75 yr old (3 doses, within 2 mo): 77.3%; ≥ 75 yr old (3 doses, after 2 mo): 78.5%; Hospitalization or death: 60-74 yr old (2 doses): 63.4%; ≥ 75 yr old (2 doses): 40.7%; 60-74 yr old (3 doses, within 2 mo): 88.4%; 60-74 yr old (3 doses, after 2 mo): 90.4%; ≥ 75 yr old (3 doses, within 2 mo): 77.3%; ≥ 75 yr old (3 doses, after 2 mo): 78.5%

and evade the vaccine[46,47,50-53]. Therefore, the tangible effect of vaccines can be substantially different from the real-world which may not necessarily illustrate the authentic effectiveness of vaccines. Furthermore, although interventional studies such as clinical trials are more methodologically sound, observational studies are more reliable since they produce practical and realistic results that are grounded from real-world experiences.

By focusing on Delta and Omicron variants, we hypothesize that much of the previous research on vaccine effectiveness only included earlier variants which may have skewed the results for newer and more dominant variants like Delta and Omicron. We also aim to provide value in understanding the effectiveness of mRNA vaccines by comparing their effectiveness in real-world settings. While the results in this study reported a marginal difference in effectiveness between Moderna and Pfizer-BioNTech vaccines, the minor difference on an absolute scale can be significant when considering world-wide population for vaccination[54].

Furthermore, the observed waning effectiveness of vaccine in this study supports the findings of other studies which suggested that the diminishing effectiveness of vaccine is due to the extensive abilities of COVID-19 virus to evolve and generate new variants which allow them to avoid the effects of the vaccines[51-53]. The ability of Delta and Omicron variants to elude sensitivity to antibody neutralization was observed to decline over time making the vaccine less effective[41,55-58]. Consistent to the findings of this study, this imply that 2 doses of mRNA vaccines is inadequate and only provides interim protection against COVID-19 infection, hospitalization, ICU admission and intubation, and deaths[58-61]. Because of the vaccine's natural diminishing effectiveness, the importance of booster dose to restore its efficacy is vital in providing additional protection against emerging variants[33,34,39,40,49,62-64]. This position is in line with the study conducted in an elderly long-term care facility where the effectiveness of vaccine was observed to only have improved after the second dose, along with other studies pointing out that booster dose can provide significant protection and is the most effective approach to COVID-19 prevention[59,63,65].

Strengths and limitations

This study provides useful information on the effectiveness of mRNA vaccines in the real-world settings which are not under a regulated condition of clinical trials. Specifically, the strengths of this study made use of an inexpensive design that is reproducible since it rests on an organized search strategy, strong procedure with the inclusion of literature from pre-print servers. It also included a broad range of possible outcome measures to include as many studies as possible that can provide relevant information on the topic. Furthermore, this systematic review included research studies from different parts of the world that have relatively large representatives of elderly population with longer follow up which is useful in minimizing selection bias.

The findings of this study should be cautiously interpreted due to certain limitations. First, the included literature were observational studies which have restrictions in statistical power. Second, since there is limitation to access the data used by the research studies, this study has a risk in information bias. Third, due to the missing data and estimation of some studies, a degree of misclassification further delimits this study. Fourth, in exchange of large sample sizes, this study sits on a potential bias of unmeasured confounder such as comorbidities or socioeconomic status like age and occupation, outbreak data such as location and time of test, and other risk-taking behavior modification. Finally, the use of heterogenous outcome measures creates limitation due to potential classification errors.

CONCLUSION

As a response to the rapidly evolving COVID-19 outbreak, many research studies were organized and carried out resulting in highly heterogeneous outcome measurements. From a research perspective, this heterogeneity inhibits the comparison, contrast, and integration of the results which makes data pooling across different studies problematic. Therefore, this systematic review suggests that, while pharma-

ceutical intervention like vaccination is important to fight an epidemic, utilizing common outcome measurements or carrying out studies with minimal heterogeneity in outcome measurements, is equally crucial to better understand and respond to an international health crisis. Notwithstanding these limitations, the consistent findings of this review indicated waning of vaccine effectiveness over time, implying that a large proportion of the vaccinated population, particularly the elderly, may lose protection unless booster doses are rolled out to restore the effectiveness of the vaccine (Supplementary Table 1).

ARTICLE HIGHLIGHTS

Research background

Although there has been a rise in the administration of vaccinations and booster shots, coronavirus disease 2019 (COVID-19) infections and fatalities continue to persist at a significant level. The effectiveness of these vaccines has been confirmed by multiple manufacturers and were rapidly developed for emergency use with testing conducted in controlled clinical conditions and on voluntary participants, whose characteristics may differ from those of the broader population.

Research motivation

The COVID-19 pandemic has caused an unprecedented global health crisis resulting in millions of deaths and infections worldwide. Despite the availability of COVID-19 vaccines and the administration of booster shots, the number of cases and deaths remains high. The development and clinical trials of these vaccines were conducted in controlled environments with volunteers which may not fully represent the general population. Therefore, there is a need to determine the real-world effectiveness of mRNA COVID-19 vaccines in the elderly during the predominance of Delta and Omicron variants in preventing COVID-19-related infections, hospitalizations, intensive care unit (ICU) admission and intubation, and death.

Research objectives

This study aimed to conduct a systematic review of available research articles to evaluate the effectiveness of Pfizer-BioNTech and Moderna vaccines on the elderly using infection, hospitalization, ICU admission and intubation, and death as outcome measures.

Research methods

The study utilized a combination of Medical Subject Headings (MeSH) and non-MeSH to identify relevant research articles from various databases and pre-print servers.

Research results

While clinical trial data on Pfizer-BioNTech and Moderna vaccines demonstrated high vaccine effectiveness in the elderly, the results of this study showed that vaccine effectiveness in real-world settings is marginally lower against infection, hospitalization, ICU admission and intubation, and death, with an indication of diminished effectiveness of the vaccine over time. Furthermore, 2 doses of mRNA vaccines are inadequate and only provide interim protection, emphasizing the need for booster doses to restore its efficacy.

Research conclusions

Continued monitoring and research to improve the effectiveness of vaccines and combat the virus effectively is important to evaluate vaccine efficacy in real-world settings, especially as new variants emerge. In addition, the use of highly heterogeneous outcome measures poses a challenge in comparing and integrating the results, and standardized outcome measures or minimal heterogeneity in outcome measurements are essential to better understand and respond to a global health crisis.

Research perspectives

Future research should continue to evaluate the real-world effectiveness of COVID-19 vaccines, including the efficacy of booster shots and the effectiveness of vaccines against new variants. Additionally, efforts should be made to standardize outcome measures to enable better comparisons across studies and facilitate the integration of findings. Ultimately, such research will be crucial in guiding public health policies and interventions aimed at controlling the spread of COVID-19 and in mitigating its impact on public health.

FOOTNOTES

Author contributions: Palalay H conceived the manuscript from study design, literature search, study selection process, data extraction, analysis, and synthesis; Tafuto B reviewed the draft, added critical comment and intellectual content, and participated in most of the study steps; Vyas R provided additional input and guidance; All authors read and approved the final manuscript for submission and take full responsibility for the content.

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SYSTEMATIC REVIEWS

Haploidentical hematopoietic stem cell transplantation as promising therapy in the improved survival of pediatric patients with leukemias and myelodysplasias

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Abstract

BACKGROUND

Haploidentical hematopoietic stem cell transplantation (Haplo-HSCT) is often performed in children with hematologic malignancies. Faced with the gap in the literature regarding the approach to experiences related to Haplo-HSCT with pediatric patients with leukemias and myelodysplasias aged up to 18 years, there was an interest in exploring the clinical outcomes of patients undergoing this treatment.

AIM

To identify and summarize the scientific contributions available on Haplo-HSCT performed in the last 10 years in children and adolescents with myeloid and lymphoid leukemias and myelodysplasias, aged up to 18 years.

METHODS

This is a descriptive systematic review. We extracted data including characteristics of participants, health condition, characteristics of the donation, conditioning regimen, recurrent clinical complications and clinical outcomes. The Virtual Health Library Brazil, PubMed, EMBASE, and SciELO platforms were used, finding a total of 1052 studies. After the eligibility criteria and complete reading of the texts, 18 articles were included for analysis.

RESULTS

The total sample of all study cohorts was 1825 patients, mostly male, the highest reported median age was 15.0 years and the lowest was 1.2 years. Acute graft-versus-host disease and chronic graft-versus-host disease were observed in almost all studies. Relapse, graft rejection and delayed immune recovery were identified as major clinical challenges. Pre-transplant minimal positive residual disease was identified in 288 patients. Infections are also among the main clinical complic-

ations, viral, bacterial and fungal infections being reported. It is observed that in the 5-year interval, the lowest rates of EFS and overall survival (OS) were 29.5% and 68.0%, respectively. While, the highest rates of EFS and OS, in the same interval, were 80.1% and 81.0%.

CONCLUSION

Haplo-HSCT represents a promising therapy, considering the potential number of possible donors and the conditioning and treatment platforms that can be offered. The results obtained show that this type of transplant has a strong antileukemic effect, with generally favorable OS rates. Overcoming relapse as the first cause of transplant failure is the great clinical challenge.

Key Words: Haploidentical; Stem cell transplantation; Children; Cancer; Treatment outcome; Prognosis

Core Tip: In recent years, the number of children under 18 years of age with leukemias and myelodysplasias undergoing haploidentical hematopoietic stem cell transplantation has increased. This type of transplant has been shown to be a promising therapy due to the availability of potential donors. The main objective is to identify the scientific contributions available on haploidentical hematopoietic stem cell transplantation performed with this audience. It has been observed that prognostic factors such as treatment platforms, cytogenetic abnormalities and disease status exert a strong influence on the clinical outcomes of transplant patients. Other variables can be obtained to collaborate with risk stratification and donor selection approaches.

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INTRODUCTION

Allogeneic hematopoietic stem cell transplantation (Allo-HSCT) has been shown to be a curative option for children with malignant and non-malignant diseases[1,2]. In this type of transplant, the progenitor cells come from genetically distinct donors, who may be related or unrelated and with human leukocyte antigen (HLA) matching or HLA partially matching. The ideal donors for hematopoietic stem cell transplantation are HLA-matched siblings or matched unrelated donors (MUD-HSCTs), but only approximately 30% of patients will have a matched sibling donor and 33% of patients will have a MUD-HSCT[1].

Haploidentical HSCT (Haplo-HSCT), a type of allogeneic transplant, represents a promising therapy in this prospect, as this type of transplant is performed with a partially HLA-matched related donor, which is available in 95% of the cases[3]. Related donors can be a father, mother, sibling or son. This transplant has a strong antileukemic effect, the graft-versus leukemia (GVL), which contributes to a lower tendency to relapse. However, due to its nature, the occurrence of clinical complications is common, such as complete rejection of the graft, the development of graft-versus-host disease (GvHD) and relapses[2,4].

The main platforms of Haplo-HSCT are *ex vivo* grafts of depleted T cells (TCD) and T- cell-filled grafts followed by post-transplantation cyclophosphamide (PT-Cy). The first is associated with a great limitation of the development of GvHD, but with slow immune reconstitution and infectious complications. While PT-Cy is associated with excellent immune reconstitution, a low incidence of serious opportunistic infections[3] and it has a more attractive cost-benefit ratio, as it does not require specific technical knowledge. There is also the infusion of unmanipulated grafts with administration of antithymocyte globulin (ATG). This platform consists of activating the donor with granulocyte colony-stimulating factor; intensified post-transplant immunosuppression with cyclosporine, methotrexate and mycophenolate mofetil; inclusion of ATG in a combined graft of bone marrow and peripheral blood[5].

Haplo-HSCT has been frequently performed in children with hematological malignancies[6]. When considering the highest incidences of childhood malignancies, it is observed that acute lymphocytic leukemia (ALL) is responsible for approximately 70% to 80% of childhood leukemia cases and acute myelogenous leukemia (AML) is responsible for approximately 15% to 20%[7-9]. In addition, among other malignancies, myelodysplastic syndrome (MDS) has a very strong interface with the neoplasms mentioned and that, although its incidence is more common in adults, the chance of myelodysplasia

evolving to more advanced forms and AML is greater in children. Therefore, many pediatric patients with MDS also are submitted to Haplo-HSCT[2,3].

Regarding the state of the art on allogeneic transplants, it should be noted that there are few publications involving the pediatric public aged up to 18 years[10]. In this perspective, we had the interest in exploring the clinical outcomes of pediatric patients with leukemias and myelodysplasias undergoing the Haplo-HSCT. For this, we carried out a systematic review, whose general objective is to identify and summarize the scientific contributions available on haploidentical hematopoietic stem cell transplants performed in the last 10 years in children and adolescents with myeloid and lymphoid leukemias and myelodysplasias, aged up to 18 years.

MATERIALS AND METHODS

We followed Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines, which consists of a 27-item checklist and a flow chart for the conduction and reporting of this systematic review[11].

Search strategy

This is a descriptive systematic review, which sought to analyze the scientific contributions available on Haplo-HSCT performed in the last 10 years with selected pediatric audience. To elaborate the guiding question, the strategy PICO-acronym to Patientes, Interventation, Comparation and Outcomes-was used [12]. Therefore, the research question that was used to guide the review was: "What is the efficacy and safety of haploidentical hematopoietic stem cell transplantation performed with the pediatric public with leukemias or myelodysplasias?".

The electronic search for articles was carried out on November 20, 2022 in the Virtual Health Library Brazil (VHL) and on the PubMed website, using the keywords selected according to the classification of Health Sciences Descriptors (DeCS): Cancer, children, transplant, and haploidentical. The Boolean operator "AND" was used. Inclusion criteria were applied, the first being the filter "language-English", "language-Spanish", and "language- Portuguese"; and the second, selection of the 10-year period (2012-2022). Forty-one results were found in VHL and 549 in PubMed, totaling 590 articles, all in English. After crossing the bases, 31 repeated articles were discarded (Figure 1).

For the analysis of the 559 articles, the abstracts were read based on the exclusion criteria: Other languages, review studies, case reports, experimental studies, paid articles, other health conditions and age over 18 years old. This step was performed by a pair of reviewers, independently, and all disagreements were resolved by consensus.

It is important to emphasize that articles that included a mixed audience with children and adults over 18 years of age were also discarded, due to the central objective of analyzing the clinical results separately. In addition, paid studies that did not allow the reading of articles through access by the Federated Academic Community of institutional link of the authors of the work were excluded. Finally, it remains to inform that the experimental studies included: Randomized clinical trials, prospective clinical trials, controlled tests and control cases, all with clinical intervention.

The order of exclusion criteria was followed: Types of study, paid articles, health condition and age. The following were discarded at this stage: 59 review articles and meta-analyses, 64 case reports, 112 experimental studies, 117 paid articles without institutional access, 55 articles on other clinical conditions and other hematological neoplastic conditions, 15 studies with mixed age and 19 with age outside the established age range. Qualitative studies, editorials, annals, reports and comments were also excluded. These other types of study, together, totaled 18 articles.

In this perspective, 100 articles were included for full text reading. However, 10 articles were excluded for not providing the full text for free and 02 unavailable studies were also discarded. After the complete reading, 72 articles were excluded for deviating from the eligibility criteria (Figure 1). The final sample included 16 articles.

A new search was performed in other databases, on April 4, 2023. For this, the same descriptors were used, as well as the same Boolean operator, the language inclusion criteria and the 10-year interval used in the previous research. The new search was carried out in the EMBASE and SciELO databases. In the last base, no results were found. At EMBASE, the platform filter "Articles" and "Erratum" was also used to select materials. There were 462 results found. However, with data crossing, 265 articles were excluded due to repetition.

After completing the reading of titles and abstracts, 174 articles were excluded due to the type of study criteria, mixed age, other clinical conditions involved and availability of the article (Figure 1). As a result, 23 articles were read in full, but only 2 studies metal eligibility criteria. In this context, with the results already obtained from the first search, 18 articles were included for analysis in this review. Among them, the types of observational studies involved were: Retrospective, retrospective comparative, and prospective cohort studies.

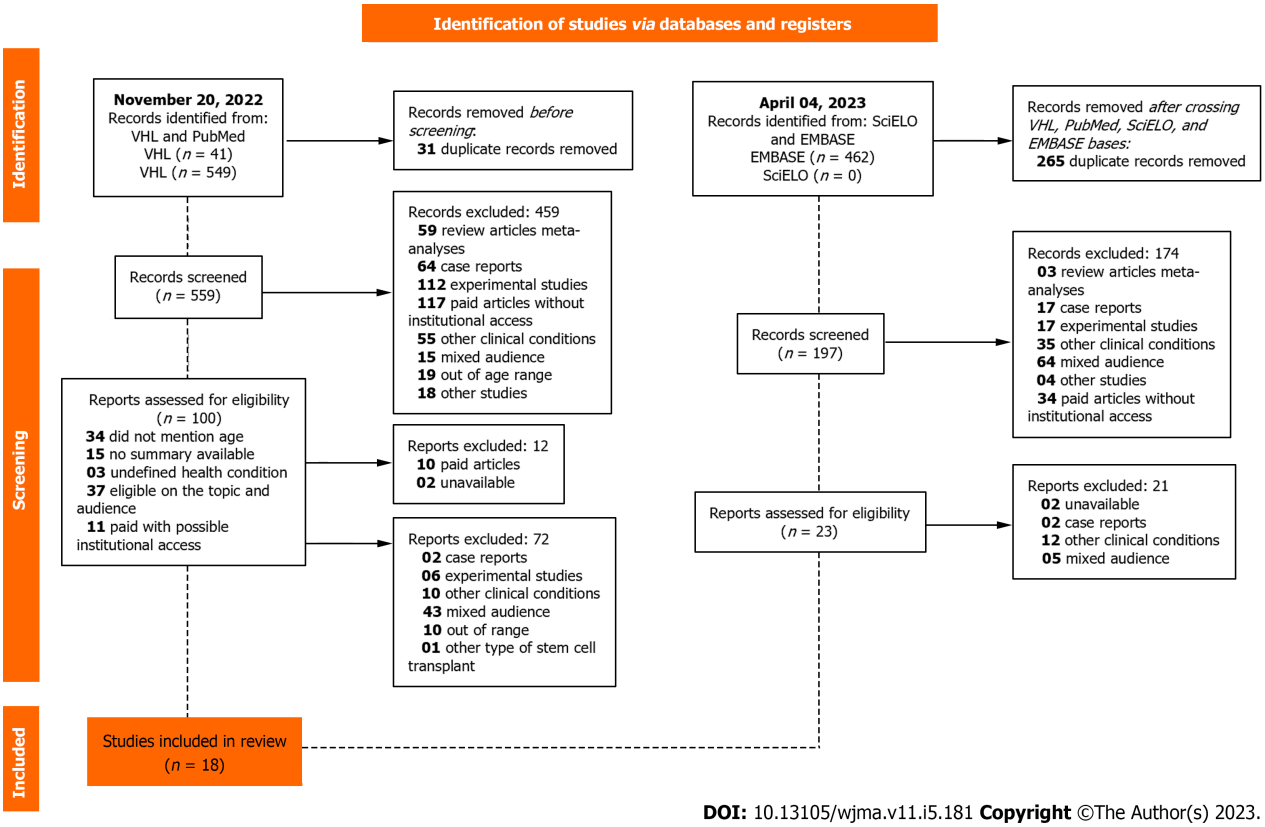

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Figure 1 Flowchart of studies selected for inclusion in the review following Preferred Reporting Items for Systematic Reviews.

Data extraction

For data extraction, a spread sheet was prepared in advance for analysis of patients and treatment, which included: (1) Participants: Number of patients, age group, gender; (2) health condition: The type of hematological malignancy; (3) characteristics of the donation: source of cells; (4) intervention: Conditioning regimen; (5) recurrent clinical complications: Types of complications; and (6) clinical outcomes: The overall survival (OS) and event-free survival (EFS) and the main reasons for death of patients.

In all articles, data on the age of the patients were obtained through the available tables, verifying the age range surveyed. In comparative studies, when possible, data were extracted from the public that received the Haplo-HSCT separately. The presentation of the statistical results of OS and EFS will also be directed to the Haplo-HSCT data of the included studies. Thus, OS and EFS rates, which have Haplo-HSCT results separately, will be presented according to their analysis intervals.

Evaluation of the quality of studies

For analysis of the studies, a survey of methodological aspects was carried out, with the authors' names, journal, year of publication, country where the study was carried out, study design, time of analysis and purpose of the study. The risk of bias of the selected studies was assessed using the Cochrane tool: Risk of Bias In Non-randomized Studies-of Interventions (ROBINS-I)[13].

The ROBINS-I presents seven domains that provide theoretical support for detecting factors that can lead to confounding when analyzing a patient's outcome, as well as enabling the analysis of possible biases in the selection of participants, performance of interventions, deviations from usual practice, availability of data, assessment of measures and reporting of studies. In this step, two reviewers, independently, assessed each domain and managed to classify each study as low, moderate, serious or critical risk, based on the platform's guidelines, as can be seen Figure 2.

In order to analyze the clinical results, the factors that influence the prognosis of patients submitted to allogeneic transplants were considered for the detection of the confounding domain[14]. These factors were divided into: Pre-transplant, peri-transplant and post-transplant. In pre-transplantation, the disease status, age and sex of the patient, information about donors and source of cells were considered. In the peri-transplantation, it was verified if there was information on the conditioning regimen, prevention of GvHD, the number of cells infused. In the post-transplant period, information on the development of acute and chronic GvHD was considered.

For all factors, the existence of variables that could statistically assess this domain was verified, including: The *P* value for gender and age of patients, source of cells and donors; the immunopheno-

Figure 2 Assessment of the risk of bias of studies in each domain of the tools Revised Cochrane Risk of Bias In Non-randomized Studies-of Interventions (ROBINS-I).

typing, white blood cell counting, platelet counting, percentage of blasts, hemoglobin levels, chimerism, cytogenetic techniques and molecular genetics were also observed, the last two when it was necessary. Thus, the indication of the factor and the establishment of the variable for its evaluation were classified as low-risk bias, while the absence of both was considered as critical condition.

RESULTS

Characteristics of the studies

The studies were published between 2014 and 2022, with retrospective and prospective analyses. Thus, in retrospective analyses, the interval between articles was from 1988 to 2021; while in prospective analyses, the public was analyzed between 2011 and 2019. The research was concentrated in seven countries: Korea, China, Italy, Colombia, Spain, Germany and Japan. It is noteworthy that China was responsible for 8 publications (Table 1).

Table 1 Methodological aspects: General characteristics on the studies included

Ref.	Journal	Country	Study designs	Study analysis time	Objective
Kim *et al*[15], 2021	*British Journal of Haematology*	Korea	Retrospective	2009-2020	To analyze genetic abnormalities in JMML to evaluate the genetic profile of this rare paediatric leukaemia in a single Korean institution
Hong *et al* [16], 2022	*Transplan tation and Cellular Therapy*	Korea	Retrospective comparative	2013-2020	To compare outcomes in children and adolescents with high-risk acute leukemia after a busulfan-based myeloablative conditioning regimen along with HRD HSCT with PT-Cy or MUD HSCT
Bertaina *et al* [17], 2018	*Blood*	Italy	Retrospective	2010-2015	To report the outcome of children with acute leukemia who received either UD-HSCT or αβhaplo-HSCT
Bai *et al*[18], 2020	*Leukemia Research*	China	Retrospective	2008-2018	To investigate the clinical characteristics, outcomes, and effects of HSCT (especially haplo-HSCT) among non- infant children with t(v;11q23)/MLL-r B-ALL
Ruggeri *et al* [19], 2021	*Transplan tation and Cellular Therapy*	Italy	Prospective cohort	2011-2019	To analyze the outcomes of unmanipulated haploidentical Transplantation using PT-Cy in pediatric patients with acute lympho-blastic leukemia
Sun *et al*[20], 2015	*European Review for Medi cal Pharmaco logical Sciences*	China	Retrospective	2002-2012	To discuss the effect of transplantation and the difference in treatment effect among children having different donor patterns, aiming to identify the prognostic factors
Sano *et al*[21], 2021	*Frontiers in pediatrics*	Japan	Retrospective	2009-2019	To aimed to evaluate the efficacy of T-cell replete HLA-HSCT for pediatric RR-BCP-ALL
Paina *et al* [22], 2018	*Cellular Therapy and Transplantation*	Germany	Prospective cohort	2006-2016	To assess efficiency of haplo-HSCT performed with non-manipulated grafts of children and adolescents with high-risk acute leukemias. In this respect an efficiency study of haploidentical GVHD was performed at our clinic in children and adolescents with high-risk ALL and AML, at maximal observation terms of 10 years
Mo *et al*[23], 2016	*Internatio nal Journal of Cancer*	China	Retrospective comparative	2011-2015	To compare the therapeutic effects of single UCBT and unmanipulated haplo-HSCT in high-risk ALL children
Wang *et al* [24], 2020	*Journal of Internatio nal Clinical Cytometr y Society*	China	Prospective cohort	2011-2016	To determine the impact of pre- and post-MRD status as well as peri-transplant MRD kinetics on clinical outcomes focused on children with ALL who received haploidentical allografts
Zhang *et al* [25], 2022	*Chinese Medical Journal*	China	Retrospective comparative	2012-2018	To explore the effect of allo- HSCT (especially haploidentical HSCT) on improving survival and reducing relapse for high-risk childhood T-ALL in CR1 and the prognostic factors of childhood T-ALL in order to identify who could benefit from HSCT
Zheng *et al* [26], 2020	*Cancer Communi cations*	China	Retrospective comparative	2013-2017	To compare the survival outcomes between high-risk AML children who underwent either unmanipulated HID-SCT or ISD-SCT at three large Chinese SCT centers
Trujillo *et al* [27], 2021	*American Society For Transplan tation and Celular Therapy*	Colombia	Retrospective	2012-2017	To decrease the toxicity associated with the addition of 100 mg/kg of cyclophosphamide to a myeloablative regimen while maintaining a good antileukemic effect and a good engraftment rate, using an intermediate-intensity regimen
Yang *et al*[28], 2022	*Hematology*	China	Retrospective	2015-2021	To investigate the outcomes and prognostic factors of pediatric AML patients with *KMT2A* rearrangements who were treated at our institution over a 5-year period
Bai *et al*[29], 2022	*BMC cancer*	China	Retrospective	2014-2019	To explore the role of allo- HSCT (especially haploidentical-HSCT) in the treatment of paediatric patients with MLL-r AML in CR1 and investigated the prognostic factors of these patients
Miyamura *et al*[30], 2019	*Leukemia Research*	Japan	Retrospective	1988-2011	To investigate the outcomes and prognostic factors of AML with KMT2A rearrangement treated with allogeneic HSCT
Oevermann *et al*[32], 2014	*Blood*	Germany	Retrospective comparative	1996-2013	To analyze the influence of KIR haplotypes on the outcome of children with ALL given haploidentical HSCT
Pérez-Martí nez *et al*[33], 2020	*American Journal of Hematolo gy*	Spain	Retrospective	1999-2016	To compare and analyze the feasibility and outcome of a Spanish cohort of 2 haplo-HSCT platforms in children and adolescents with high-risk hematological malignancies: PT-Cy and *ex vivo* TCD grafts

JMML: Juvenile myelomonocytic leukemia; HSCT: Hematopoietic stem cell transplantation; PT-Cy: Post-transplantation cyclophosphamide; MUD: Matched unrelated donors; RR-BCP: Relapsed or refractory B-cell precursor acute lymphoblastic leukemia; KIR: Killer cell immunoglobulin-like receptor; TCD: T cells; ALL: Acute lymphocytic leukemia.

Regarding the risk of bias in the studies, the serious-risk in the analysis of selection bias is due to the fact that some of the aspects of the attributions of the status of the intervention were determined in a way that could have been affected by the knowledge of the previous result combined with the fact that the beginning of the follow-up and the beginning of the intervention did not coincide, so that the interpretation could not be adjusted in the final analysis of the outcomes. While, in the deviations, those studies were indicated that had to switch regimens and co-interventions due to the initial responses of the patients. The changes were not balanced across intervention groups. In addition, the data and reports concern the availability of all information from participants in the interventions and demonstration of multiple analyzes and different subgroups.

Characteristics of the patients

The total sample of all cohorts of the analyzed studies was 1825 patients, considering the entire audience in the comparative studies and information on patient removal due to death before treatment (Table 2). The majority of the sample was composed of males, the highest median age reported was 15 years and the lowest, 1.2 years. The ethnicity of the participants was not a topic well explored by the authors.

Among the reported clinical conditions, the following were observed: Juvenile myelomonocytic leukemia (JMML), ALL, acute myeloid leukemia, chronic myelogenous leukemia, mixed lineage leukemia, mixed-phenotype acute leukemia and NK cell leukemia. In addition, it is verified that 1295 patients underwent Haplo-HSCT, considering the information on the withdrawal of patients from the original cohorts due to another type of donation, such as a MUD-HSCT and matched sibling donor (MSDT) (Table 2).

Regarding the type of conditioning, different types of regimens were observed, with the adoption of the Myeloablative Conditioning Regimen, some with total body irradiation, and also the Reduced Intensity Regimen. In studies that detailed the types of chemotherapy, it was observed that the main drugs used were: Busulfan, Fludarabine, Cytarabine, Cyclophosphamide, Melphalan, and Semustine (Table 3).

In addition, for the prevention of graft disease and mobilization of the BM and peripheral blood stem cells (PBSC), the interventionists of the analyzed studies used different combinations of drugs, therefore, the same study used one or more compounds. As a result, ATG was administered by 12 studies; post-transplant cyclophosphamide, 5; Cyclosporine A, 13; Methotrexate (MTX), 11; Mycophenolate mofetil (MMF), 10; Tacrolimus, 6; granulocyte colony stimulating factor, 6; and Sirolimus, 1. Two studies did not present the names of the drugs used for this purpose.

Outcomes

Recurrence, graft rejection and delayed immune recovery are the major clinical challenges that have been identified. The occurrence of hematological recurrences was observed in most of the studies, with the exception of Kim *et al*[15], in which this type of clinical complication was not explicitly mentioned. Among the authors who reported, seven studies pointed to extramedullary recurrences (EMR). Hong *et al*[16] identified extramedullary recurrence in the central nervous system, the others did not report the location of the EMR.

Acute graft-versus-host disease (aGvHD) and chronic graft-versus-host disease (cGvHD) were also observed in most of the analyses, with the exception of the study by Bertaina *et al*[17], in which there were no cases of grade III-IV or visceral aGvHD in the haploidentical transplant cohort, and two other studies that did not discuss this type of complication.

In the total sample of all cohorts of the analyzed studies, the pre-transplant minimal positive residual disease (pre-MRD+) was identified in 288 patients; while 337 patients were MRD negative (pre-MRD-). After transplants, 90 patients were identified with positive MRD (post-MRD+), 19 with reemerging MRD. However, these data are limited, considering the fact that some authors did not present the pre-transplant and post-transplant MRD status together, and also not all comparative studies that separated the results of the analyzed cohorts. In addition, eight other articles did not have either status.

It is known that immunosuppression makes the patient susceptible to infections. Therefore, infections are also among the main clinical complications, with viral, bacterial and fungal infections being reported. Among viral infections, cytomegalovirus and adenovirus were the most common. In addition, due to treatment-related toxicity, multiple organ failure, hemorrhagic cystitis, and cerebral and alveolar hemorrhages have been reported. Among organ failure, liver impairment was reported in 05 studies and 02 studies also pointed to the involvement of the gastrointestinal tract and skin. Other causes of complications include sepsis, pneumonia, and cases refractory to treatment. Other types of complications occurred in smaller numbers.

The main causes of death were relapses, graft-versus-host disease, infections and transplant-related complications. Furthermore, non-recurring mortality (NRM) was also presented in most of the studies. However, in the study by Hong *et al*[16], the group that received Haplo-HSCT did not present any cases of NRM.

The OS and EFS rates are indicated in Table 3. It is observed that in the 5-year interval, the lowest EFS and OS rates were 29.5% and 68.0%, respectively. The EFS result of 29.5% was reported in patients with transplants from a KIR A haplotype donor. In this same interval, the highest rates of EFS and OS were 80.1% and 81.0%, respectively. At the 10-year interval, OS rates were 64.7% for patients in a first

Table 2 Characteristics of haploidentical transplants identified in the studies included

Ref.	All patients, *n*	Age, yr, median	Sex, male, *n*	Condition clinic	Haplo transplant cohort, *n*	Age, yr, median	Sex, male, *n*	Source of stem cells
Kim *et al*[15], 2021	24	1.20[1]	15	JMML	14	NR	NR	PBSC
Hong *et al*[16], 2022	80	NR	51	ALL, AML, MPAL, and NK cell leukemia	35	7.00	22	PBSC
Bertaina *et al*[17], 2018	343	3.30	210	ALL, AML	98	6.60	65	PBSC[5] BM
Bai *et al*[18], 2020	38[3]	4.00	25	MLL-r B-ALL	19[4]	4.00	13	NR
Ruggeri *et al*[19], 2021	180	9.25	114	ALL	180	9.25	114	PBSC BM
Sun *et al*[20], 2015	111	10.00	73	AML, ALL, CML, and MLL	111	10.00	73	PBSC BM
Sano *et al*[21], 2021	19	10.00	12	RR-BCP-ALL	19	10.00	12	PBSC, PB + BM
Paina *et al*[22], 2018	106	7.00	65	ALL, AML	106	7.00	65	BM + PBSC BM
Mo *et al*[23], 2016	129	NR	42	HR, ALL	65	10.00	33	G-BM, G-PB
Wang *et al*[24], 2020	166	15.00	114	B-ALL and T-ALL	166	15.00	114	NR
Zhang *et al*[25], 2022	74	11.00	52	HR T-ALL	27[2]	12.00	21	BM
Zheng *et al*[26], 2020	82	NR	56	HR AML	69	12.00	42	PBSC, BM
Trujillo *et al*[27], 2021	42	11.00	24	ALL, AML, JMML, and CML	42	11.00	24	PBSC
Yang *et al*[28], 2022	21	NR	15	AML, *KMT2A* rearrangents	17	6.06	12	NR
Bai *et al*[29], 2022	44	9.00	25	MLL-r AML	37	NR	NR	NR
Miyamura *et al* [30], 2019	90	3.00	49	AML *KMT2A* rearrangents	10	NR	NR	NR
Oevermann *et al* [32], 2014	85	10.00	NR	ALL	85	10.00	NR	PBSC
Pérez-Martínez *et al*[33], 2020	192	8.60	118	ALL, AML, MDS, JMML, CML, and biphenotyipic	192	8.60	118	PBSC BM

[1]In the study, this information was given in months.
[2]Four patients had a matched sibling donor. So, only 23 patients received haplo-hematopoietic stem cell transplantation. However, Zhang *et al*[25] didn't give the age and numbers by sex separately.
[3]One patient was excluded from the analysis owing to death from pulmonary infection during induction. So, only 37 patients were analyzed.
[4]One patient received human leukocyte antigen-MUDT. So, only 18 received the haplo-transplant CR1. However, Bai *et al*[18] didn't give the age and numbers by sex separately.
[5]All patients in the haplo cohort received stem cells from peripheral blood stem cells.
JMML: Juvenile myelomonocytic leukemia; ALL: Acute lymphocytic leukemia; AML: Acute myeloid leukemia; CML: Chronic myelogenous leukemia; MLL: Mixed lineage leukemia; MPAL: Mixed-phenotype acute leukemia; NK: Natural Killer; RR-BCP: Relapsed or refractory B-cell precursor acute lymphoblastic leukemia; NR: Not related; PBSC: Peripheral blood stem cells; BM: Bone marrow; PB: Peripheral blood.

complete remission (CR1) and second CR (CR2); and 18.1% for patients transplanted beyond remission (Table 3).

It is emphasized that, in the study by Bai *et al*[18], patients in the chemotherapy regimen cohort who relapsed and opted for haploidentical transplantation had an OS rate of 57.1%. Thus, in CR2, the results were less satisfactory in relation to the results of transplants performed in CR1 in that same study. At the same time, it was observed in the study by Ruggeri *et al*[19] that patients in CR1, CR2, and CR3 had a 2-year EFS of 65.0%, 44.0%, and 18.8%, respectively. Finally, it is noted that three other studies showed an EFS rate below 50%, with an interval of 2 years in two studies and 3 years in two studies (Table 3).

Table 3 Conditioning, event-free survival and overall survival of the analyzed patients

Ref.	Haplo transplant cohort, *n*	Conditioning regimens (all cohorts)				Haplo cohort	
		I	II	III	IV	EFS (%)	OS (%)
Kim *et al*[15], 2021	14	MAC: Bu-Flu	MAC: Bu-Flu-TBI	RIC: Bu-Flu-TBI	-	NRS	NRS
Hong *et al*[16], 2022	35	MAC, Bu, Flu	MAC, Bu, Flu, and Cy	TBI after blinatumomab	-	74.4% (3 years)	88.6% (3 years)
Bertaina *et al*[17], 2018	98	MAC: Bu	MAC/TBI: TBI-based	Treosulfan based	-	62.0% (5 years)	68.0% (5 years)
Bai *et al*[18], 2020	18[1], 08[7]	MAC/chemo: Cytarabine, Cy, Bu, and semustine	-	-	-	89.5% (4 years), NRS	87.4% (4 years); 57.1% (4 years)
Ruggeri *et al*[19], 2021	180	MAC/chemo	MAC/TBI	RIC	-	38.5%[2] (2 years); 65%[3]; 44%[4], and 18.8%[5]	50.8% (2 years); 76.5%[7]; 61.2%[7]; (NRS)
Sun *et al*[20], 2015	111	MAC: Bu, cycytarabine, and Me-CCNU	MAC/TBI Cy, cytarabine	-	-	79.2% (5 years)	NR
R	19	MAC: Bu, Flu, and melphalan, TBI-based	MAC: Bu-based	RIC	-	42.1% (3 years)	57.4% (3 years)
Paina *et al*[22], 2018	106	MAC: Bu, Cy, and Lomustin	MAC, Bu-flu	MAC: Treosulfan	RIC: Melphalan; RIC: Bu	NR	33.3% (10 years); 64.7%; 18.1%, (10 years)[6]
Mo *et al*[23], 2016	65	Cytarabine, Bu, Cy, and semustine	TBI	MAC: Bu-Flu Carmustine	MAC: CyFlu-TBI	71% (2 years)	82.0% (2 years)
Wang *et al*[24], 2020	166	RIC: Cy, MTX, MMF	-	-	-	60.2% (100 d)	60.8% (100 d)
Zhang *et al*[25], 2022	23	MAC: Bu-Cy, hydroxyurea cytarabine, and methy	-	-	-	80.1% (5 years)	81.0% (5 years)
Zheng *et al*[26], 2020	69	Bu-Cy, cytarabine, semustine	Bu-Cy-Hu, cytarabine, semustine	-	-	72.9% (3 years)	73.0% (3 years)
Trujillo *et al*[27], 2021	42	RIC: Bu-Flu-TBI	RIC: Flu-Mel-TBI	-	-	46% (3 years)	56% (3 years)
Yang *et al*[28], 2022	17	Cytarabine, Bu, and Cy Me-CCNU	Cytarabine, Bu-Cy	-	-	NRS	NRS
Bai *et al*[29], 2022	37	Cytarabine, Bu-Cy, and semustine	-	-	-	65.6% (3 years)	73.0% (3 years)
Miyamura *et al*[30], 2019	10	MAC, Bu-TBI	RIC, NR	-	-	NRS	NRS
Oevermann *et al*[32], 2014	85	TBI	Non TBI	-	-	50.6%[7] (5 years); 29.5%[7] (5 years)	NR
Pérez-Martínez *et al*[33]	192	Flu-Thiotepa-Mel or Bu	TLI or TBI	-	-	49.2% (2 years)	55.1% (2 years)

[1]In the study, 18 patients in the complete remission 1 (CR1) e 8 other patients from the other cohort experiencing relapse opted for allogeneic hematopoietic stem cell transplantation (HSCT, CR2, *n* = 13, but just 8 patients opted for allogeneic HSCT).
[2]General.
[3]CR1.
[4]CR2.
[5]CR3.
[6]CR1 and CR2; patients transplanted beyond the remission.
[7]KIR B haplotype; KIR A haplotype.
NRS: Not reported separately; NR: Not reported; TLI: Traumatic lung injury; TBI: Total body irradiation; MAC: Myeloablative conditioning regimen; RIC: Reduced intensity regimen.

DISCUSSION

Based on the analysis of selected studies, this review presented the clinical results indicated of pediatric

patients with leukemias and myelodysplasias younger than 18 years old who underwent Haplo-HSCT. Until the moment, there are few published reports on the use of Haplo-HSCT in selected pediatric populations. In our review, the total sample in the analyzed studies of patients undergoing Haplo-HSCT was 1295 patients, in which both favorable outcomes and poor prognostic factors were observed. Haploidentical transplantation is often indicated in more severe cases and for patients in second remission according to the time and place of disease recurrence[19], however, studies have indicated efficient results for patients treated in first complete remission and with early referral[19,20-22].

Ruggeri *et al*[19] indicate the importance of disease status as one of the most important prognostic factors influencing the risk of disease recurrence and the probability of EFS and OS. In that study, patients in CR1, CR2, and CR3 had 2-year EFS of 65.0%, 44.0%, and 18.8% and 2- year OS of CR1 and CR2, 76.5% and 61.2%, respectively. These results are consistent with the study by Bai *et al*[18], in which patients in CR1 had a 4-year OS of 87.4% and patients in CR2 had an OS at the same interval of 57.1%. Thus, both studies indicate the worsening of the patient's prognosis as the disease progresses and indicate that the results show the feasibility of Haplo-HSCT for patients in CR1 and CR2. In contrast, Mo *et al*[23] found no relationship between pre-transplant disease and EFS, however, the authors point to the low number of patients in non-remission or relapse at the time of transplantation, which limits their analyses.

Pre-transplant MRD status is also indicated as a poor prognostic factor, often related to an increased probability of recurrence[19,23,24]. In our review, 288 patients were identified with pre-MRD+ in the analyzed studies. These patients had higher recurrence rates than the pre-MRD- group. However, in the analysis by Zhang *et al*[25] and Bai *et al*[18], there was no clear impact predictor at the level of MRD after induction. That is, despite a trend towards lower OS/EFS and higher cumulative incidence of relapse in patients with MRD+ after induction, the results were not statistically significant[18]. The authors presented as justifications the limited number of patients in the analysis and the effectiveness of allo-HSCT in the impact of the MRD level after induction[18].

However, in our series, the data extracted on MRD was limited, as not all studies explored this prognostic factor and few authors provided the comparison and follow-up of cohorts with pre-MRD+/pre-MRD- and post-MRD+/post-MRD-. Thus, there is little information on the effects of MRD on outcomes in Haplo-HSCT, although MRD can be configured as a transformative approach in risk stratification[18].

The graft *vs* leukemia (GVL) effect is related to chronic GvHD[23]. Studies indicate that the GVL effect is stronger in patients who receive haploidentical transplantation[23,26]. In a multivariate analysis in the study by Mo *et al*[23], mild and moderate cGvHD was associated with a significant improvement in the survival of patients who presented with transplantation, possibly due to the GVL effect, and that, despite the high incidence of cGvHD, there was no significant increase in the risk of NRM in the Haplo-HSCT group. However, the same authors alert to the fact that intense immunosuppressive therapy, which has been correlated with severe cGvHD, can revoke the effector cells of the GVL effect and impair the quality of life of these patients.

When analyzing aGvHD, the study by Bertaina *et al*[17] was noteworthy. There were no cases of grade III-IV or visceral aGvHD in the haploidentical transplant cohort[17]. In this study, the authors performed a multicenter scaled analysis to compare the efficacy of αβhaplo- HSCT and MUD-HSCT in a cohort where the TBI-based conditioning regimen was frequently used. Furthermore, in that study, there was a lower risk of NRM in αβhaplo-HSCT recipients compared to HLA misMUD-HSCTs, the authors attributed to the fact that chronic GvHD was also limited.

Other variables such as age have been identified as prognostic factors in some studies. In the study by Zhang *et al*[25], children with ALL aged ≥ 10 years was an independent risk factor that affected 5-year OS and EFS rates. Advanced age was also associated with a poor prognosis with a higher risk of extramedullary recurrence, according to Ruggeri *et al*[19]. However, compared to all the data, it is noted that few studies have identified the statistical significance of advanced recipient age. No statistical significance was found for the recipient's gender either.

The studies Indicate the association between high initial leukocyte count and risk of recurrence[25] and, in Ruggeri *et al*[19], the use of PBSC was associated with a significantly lower OS, with a higher risk of NRM. While, Trujillo *et al*[27] indicate that PBSC is associated with a lower number of relapses. In this regard, as the source of graft cells is a modifiable factor, it would be interesting if the source was better researched, considering the characteristics of patients and diseases.

Genetic abnormalities and rearrangements

Cytogenetic abnormalities are important prognostic factors in cases of hematologic malignancies. Thus, understanding these manifestations can contribute to decisions regarding treatment strategies[15,25]. In this regard, our study brought, based on retrospective analyses, the presentation of the effects of cytogenetic alterations in high-risk myeloid and lymphoid leukemias, such as rearrangements of mixed-lineage leukemia genes, and in myelodysplastic syndromes with rare genetic profiles.

Therapeutic considerations range from observation to allogeneic stem cell transplantation, depending on the genetic subtype. In the case of JMML, a very aggressive form of MDS, Kim *et al*[15] showed, in their analyses, that allo-HSCT is still presented as the only curative treatment option for most patients and that patients frequently have poor EFS rates. In that study[15], patients with mutations involving

RAS pathway genes and somatic mutations in non-receptor protein tyrosine phosphatase type 11 were the most common mutations identified, and had a 5-year EFS of 72.9% and 41.7%, respectively. Among these patients, 14 patients received Haplo-HSCT. The authors drew attention to the fact that cytogenetic changes influence disease progression, rather than the onset of leukemia, which makes it valuable for predicting disease outcomes.

In the same perspective, the presence of cytogenetic abnormalities in 11q23 involving lysine-specific methyltransferase 2A (KMT2A) has been associated with adverse outcomes and higher rates of early death and relapse even after allogeneic hematopoietic stem cell transplantation[28,29]. Its occurrence is more common in children than in adults, and the prognostic value influencing outcomes in pediatric AML is associated with the fusion partner gene. The KMT2A/MLLT3 fusion resulting from t(9;11)(p22;q23) KMT2A is the most common rearrangement in children. However, it is the t(6,11) and AF10 translocation partners in t(10,11) that are often associated with poor prognosis[25].

In the study by Miyamura *et al*[30], no patient with t(6,11) remained alive in CR and only 1 patient with t(10,11) remained alive in CR, which corroborates the findings in the literature. However, the authors note that the t(9,11) translocation partner was found more frequently in their patients and that their results did not differ significantly from other 11q23 abnormalities. Although the lack of difference in transplant results was justified based on the retrospective analysis and the possible biases generated, this is something that deserves to be further studied.

In this regard, Yang *et al*[28] noted the high occurrence of KMT2A rearrangements in childhood AML and how the prognosis of children with t(9;11)(p22;q23) remains controversial. Thus, when they performed a retrospective investigation on the outcomes and prognostic factors of pediatric AML patients with KMT2A rearrangements, it was identified that approximately 31.3% of the investigated children had the KMT2A/MLLT3 fusion gene. Some of these children underwent hematopoietic stem cell transplantation, where four received donations from compatible sibling donors and another seventeen received haploidentical transplants. As a result, presented, they had EFS between the two groups of $P = 0.303$. Therefore, EFS rates were not statistically significant among patients who received haplo-HSCT and full-matched HSCT, which indicates that, in the absence of a suitable fully matched donor, children with high-risk AML who carry mutations in the KMT2A gene, may accept haploidentical hematopoietic stem cell transplantation.

KIR haplotypes impacts

It has been observed that the presence of donor-derived alloreactive NK cells influences the outcome of haploidentical hematopoietic stem cell transplantation, given that among HLA non-identical donors and recipients, donor NK cells that encounter recipient target cells without an HLA class I allele present in the donor's HLA genotype can exert antileukemic effects[31]. Among these effects are lower rates of relapses, graft failure and GvHD, which contributes to patient survival[31]. In this context, it was discussed about the response of patients to treatment considering the influence of killer cell immunoglobulin-like receptors (KIRs) present on NK cells.

The expression of inhibitory KIR receptors is responsible for the alloreactivity of NK cells in allogeneic hematopoietic stem cell transplantation[31,32]. Oevermann and other collaborators[32] presented a series of 85 patients with high-risk ALL confirmed by Haplo- HSCT, where 74% of donors had KIR B haplotype and 26.0% of the donors had KIR A haplotype. Patients transplanted from the B haplotype donor had a 5-year EFS of 50.6%, while patients transplanted from the A haplotype donor had 29.5%.

This was also observed in the study by Pérez-Martínez *et al*[33], where early reconstitution of NK cells was reported on the *ex vivo* TCD platform and related prognoses with the donor KIR B haplotype, while the KIR A haplotype increased the probability of relapse on the PT-Cy and *ex vivo* TCD platforms. In this regard, the authors drew attention to the inclusion of genotyping when choosing donors, with preferential selection of KIR B haplotype donors due to the results observed.

Therapeutic and regimens effects

Discussions about the main platforms of Haplo-HSCT and the type of conditioning regimen that patients are submitted during treatment are points of evaluation between the authors. In the records of Pérez-Martínez *et al*[33], in an analysis of morbidity and mortality associated with GvHD, considerations were found regarding *ex vivo* grafts of depleted TCD and grafts filled with T cells followed by PT-Cy. Thus, although a higher incidence of aGvHD grades I-II was noted in patients treated with the PT-Cy platform, the results that include OS, EFS and recurrence demonstrated that there are no statistical differences between both grafts in the outcomes analyzed by the authors. The great challenge that remains, on both platforms, is overcoming relapse as the main cause of transplant failure[33].

Treatment platforms have been widely studied. Studies point to the impact of high doses of purification of CD34 cells on GvHD, with a reduction and decrease in cases. However, this technique has a high transplant-related mortality due to the delay in immune reconstitution, which promotes a high risk of infection during the first months after transplantation. In this perspective, another type of purification, which has been widely used, is the partial depletion of T cells, such as αβ, which has shown optimistic results, since this technique maintains some subsets of T cells, such as γδ T cells, NK cells and memory T cells without increasing GvHD. Regarding the PT-Cy approach, which has been shown to be

effective in reducing GvHD, there is the advantage of not requiring *ex vivo* manipulation of the graft. However, PT-Cy requires prolonged immunosuppression treatment[19,27,33].

With regard to conditioning, discussions of myeloablative (MAC) and low-intensity (RIC) regimens have been contrasting. Bertaina and other authors[17] pointed to a low incidence of graft failure (2%) in the αβhaplo-HSCT group with the use of a fully MAC conditioning regimen and associated the regimen as a possible explanation for the lower incidences of relapse in the analyzed patients. As in the studies by Ruggeri *et al*[19], the MAC regimen was associated with significantly longer GvHD/relapse-free survival. While Trujillo *et al*[27] point out that the MAC regimen is often associated with acute and long-term toxicities, such as secondary malignancies and increased acute mortality, and that the combination of a RIC with haploidentical cells using the PT-Cy platform has a very strong antileukemic effect. From this perspective, studies that analyze MAC and RIC regimens and their contribution to patients' quality of life are needed.

CONCLUSION

Haplo-HSCT has been shown to be a promising therapeutic option. In recent years, the number of Haplo-HSCT has increased with the pediatric public under the age of 18, however, publications do not keep up with this pace. This review was performed based on retrospective and prospective data; thus, the methodological aspects of the studies may have influenced the analysis. Therefore, randomized clinical trials and meta-analyses should be encouraged in order to confirm the reported findings.

When exploring the published studies, it was observed that prognostic factors such as treatment platforms, cytogenetic abnormalities and disease state exert a strong influence on the clinical outcomes of transplanted patients and other variables can be obtained in order to collaborate with risk stratification and selection approaches of donors. Nevertheless, the information extracted about age and source of stem cells as prognostic factors is insufficient to provide a conclusion, considering the counterpoint of information across the studies presented.

The indication of Haplo-HSCT for patients in first complete remission is evident. Studies have indicated efficient results for patients treated at this stage and with early referral, with significantly important and different survival rates. Thus, it is noted that disease status as one of the most important prognostic factors influencing the risk of disease recurrence and the probability of EFS and OS.

One of the clinical challenges is the delay in immune recovery. This delay depends on the chosen treatment platform, since in grafts with highly purified CD34 cells there is a limitation of cell reconstitution. While on the PT-Cy, reconstitution has greater speed and lower financial cost, but with prolonged immunosuppression treatment, and, in partial T-cell depletion, some T-cell subsets are received without increasing GvHD. In this perspective, there are pros and cons between the treatment platforms, and, therefore, the characteristics of the disease and the patients to be transplanted must be considered.

Relapse, identified as a primary transplant failure, was the most recurrent clinical complication, with many factors contributing to relapse. Among these factors, a limitation of this review was the analysis of MRD status, with pre-MRD+/pre-MRD- and post-MRD+/post- MRD- cohorts. Here, although pre-MRD+ was pointed out as a poor prognostic factor, the numbers were too few for a complete analysis. Thus, studies that seek to identify the effectiveness of Haplo-HSCT in the impact of the MRD level after induction should be encouraged.

In summary, Haplo-HSCT represents a promising therapy, considering the potential number of possible donors and the accommodation and treatment platforms that can be offered. The results obtained show that this type of transplant has a strong antileukemic effect, with generally accepted rates of survival. Overcoming relapse as the first cause of transplant failure is the great clinical challenge.

ARTICLE HIGHLIGHTS

Research background

Haploidentical hematopoietic stem cell transplantation (Haplo-HSCT) has been performed in patients with different hematological malignancies. This type of transplant is performed with a related donor with partially HLA matching; therefore, it has a high availability. In recent years, the number of children with leukemia and myelodysplasia submitted to Haplo-HSCT has increased. However, there are few evaluations on the efficacy and safety of this treatment, considering only the pediatric public under 18 years of age.

Research motivation

The availability of donors in the Haplo-HSCT has been listed as one of the main reasons for carrying it out with the pediatric public, arousing the interest of researchers in evaluating the benefits of this treatment. In this sense, we sought to assess the factors that influence the prognosis of patients, complic-

ations and clinical outcomes.

Research objectives
To identify and summarize the scientific contributions available on haploidentical hematopoietic stem cell transplants performed in the last 10 years in children and adolescents with myeloid and lymphoid leukemias and myelodysplasias, aged up to 18 years.

Research methods
This is a descriptive systematic review. The VHL, PubMed, EMBASE and SciELO databases were consulted, but the results were only obtained in the first three. Based on the eligibility criteria, 18 articles were included in this review. For data extraction, the characteristics of the patients and treatment were sought, which included the number of patients, age group, gender, health condition, characteristics of the donation, conditioning regimen and recurrent clinical complications.

Research results
The studies included 1825 patients, most of whom were men, although gender was not an independent factor for the patients' prognosis. Regarding age, the data are inconclusive, as well as for the source of stem cells. Pre-transplant DRM status and intense immunosuppressive therapy are also factors that impact patient prognosis. The main complications observed were acute graft-versus-host disease, chronic graft-versus-host disease and infections. Clinical challenges are relapse, graft rejection and delayed immune recovery. In general, the studies indicated good results for patients treated in first complete remission and with early referral.

Research conclusions
The indication of Haplo-HSCT for patients in first complete remission is evident. Studies have shown efficient results for patients treated in this phase and with early referral, with significantly important and differentiated survival. In this perspective, considering the potential number of potential donors and the treatment platforms that can be offered, Haplo-HSCT appears to be a promising therapy. Randomized clinical trials and meta-analyses should be performed to confirm the reported findings.

Research perspectives
The pre-MRD+ was pointed out as a poor prognostic factor, as well as age and cell source, but the numbers were too few for a complete analysis. Thus, it is suggested that researchers consider these aspects and include the MRD status, with pre-MRD+/pre-MRD- and post-MRD+/post-MRD- cohorts. The analysis of the influence of the ethnicity of the patients must be done, this will contribute even more to the evaluation of the Haplo-HSCT.

FOOTNOTES

Author contributions: Cardoso Brito ACC, Oliveira Carneiro Ribeiro E, and Freire de Melo F equally contributed to this paper with the conception and design of the study, literature review and analysis, drafting and critical revision and editing, and final approval of the final version; and all authors agree to be accountable for all aspects of the work in ensuring that questions that are related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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SYSTEMATIC REVIEWS

Exploratory systematic review and meta-analysis on period poverty

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Abstract

BACKGROUND

Period poverty is a global health and social issue that needs to be addressed. It has been reported that many females compromise their education, employment, and social commitments during their menstruation days due to a number of reasons, including lack of access to toilets or menstrual products.

AIM

To provide a comprehensive understanding on period poverty, including outcomes associated with menstruation.

METHODS

All observational and randomised clinical trials reporting menstruation challenges, menstrual poverty and menstrual products were included. Our search strategy included multiple electronic databases of PubMed, Web of Science, ScienceDirect, ProQuest and EMBASE. Studies published in a peer review journal in English between the 30th of April 1980 and the 30th of April 2022 were included. The Newcastle-Ottawa Scale was used to assess the risk of bias of the systematic included studies. Pooled odds ratios (ORs) together with 95% confidence intervals (CIs) are reported overall and for sub-groups.

RESULTS

A total of 80 studies were systematically selected, where 38 were included in the meta-analysis. Of the 38 studies, 28 focused on children and young girls (*i.e.*, 10-24 years old) and 10 included participants with a wider age range of 15-49 years. The prevalence of using disposable sanitary pads was 45% (95%CI: 0.35-0.58). The prevalence of menstrual education pre-menarche was 68% (95%CI: 0.56-0.82). The prevalence of good menstrual hygiene management (MHM) was 39% (95%CI: 0.25-0.61). Women in rural areas (OR = 0.30, 95%CI: 0.13-0.69) were 0.70 times less likely to have good MHM practices than those living in urban areas.

CONCLUSION

There was a lack of evidence, especially from low- and middle- income countries. Further research to better understand the scope and prevalence of period poverty should be considered. This will enable the development of improved policies to increase access to menstrual products and medical support where necessary.

Key Words: Period poverty; Menstruation; Mental health; Menstrual education; Menstrual hygiene

Core Tip: Period poverty is an important health issue, impacting social and psychological wellbeing. Issues are predominantly seen in low- and middle- income countries, affected by conflicts, disasters, and economic struggles. Evidence showed a link between menstruation and prevalence of stress, anxiety, and depression. Whilst menstruation is a physical health issue, there are clear associations with mental health. Despite the global scale of period poverty, it is under-researched and is not well understood. Further research in this area will help to form healthcare policies and support for women and girls.

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INTRODUCTION

The World Health Organization (WHO) defines health as complete mental, physical, and social well-being, thus not a mere absence of a disease or infirmity[1]. For women, menstrual health is integral to maintain their overall health as menstruation occurs between menarche and menopause, which may have a significant impact on their mental, physical, and social wellbeing. Menstruation, or periods, is a biological process that is part of nearly every biological female's life and is defined as cyclical bleeding that occurs as a result of the regeneration of the uterine endometrium corpus. Clinically, the normal menstrual process is of 4 phases across a cycle of 28-35 days[2,3]. The regularity of these cycles, duration

of each of the bleeding episodes within a cycle, and the volume or heaviness of the bleed varies across women and can change throughout an individual's lifespan[2,3]. All women do not experience normal menstrual bleeding, with approximately 30% experiencing alterations to their pattern or volume of menstrual flow due to multiple aetiologies[2,4]. Many women also report symptoms such as pain, anxiety, fatigue, dysmenorrhea, and depression associated with their menstrual cycle that may require clinical involvement to diagnose potential reproductive health issues such as premenstrual dysphoric disorder, premenstrual syndrome, or endometriosis[2-4]. To promote positive health and wellbeing outcomes to all genders and clinicians, it is important to understand menstrual cycles and menstrual health that can be promoted in the first instance by way of menstrual health literacy and various public interventions such as maintaining good hygiene practices and access to menstrual products.

Access to menstrual products is as vital as access to other hygiene products. The WHO and United Nations International Children's Emergency Fund has reported that many girls miss school and put their lives on hold to remain at home during their menstruation days due to a number of reasons, including access to toilets or menstrual products[5,6]. This is commonly reported as period or menstruation poverty[7]. Period poverty is a global health issue impacting people who do not have access to hygienic and safe menstrual products. This is particularly important for regions with conflicts and disasters, which leave menstruating people with minimal or no access to safe menstrual products or clean toilets. This could lead to the use of unconventional methods to manage the bleeding such as the use of clothing, rags or sitting on old tin cans[8-10]. Ancient traditions such as Chhaupadi practices could further risk girls and women from securely managing their menstruation[11]. Chhaupadi is practiced in some far western rural regions in Nepal where young girls are banished into sheds or mud huts during menstruation or even longer as they believe this brings ill health or bad luck to the families [11]. Often these people have little or no access to washing facilities or supplies leading to health issues, including physical and psychological hardship[11,12]. Despite Chhaupadi being illegal in Nepal since 2005, Action Aid reports that it is practiced in some communities to date[12]. Whilst poverty and stigma impact the right for a girl child's education, especially in low-middle-income countries, The United Nations Educational, Scientific and Cultural Organization reports that 1 in 10 girls in Africa alone misses school during their menstruation[13]. Missing school could lead to dropping out, risking child marriage and pregnancy at a younger age, as reported by Action Aid[14].

It has been reported for many decades that menstrual poverty is associated with stigma and shame and impacts the dignity and overall wellbeing. Despite being a developed country, over 37% of women in the United Kingdom (UK) have experienced period shaming by way of isolation, bullying and jokes, based on an Action Aid survey report[15]. Approximately 40% of women reported being humiliated by their partners, while over half of UK women said they were embarrassed when they got their periods for the first time. In addition, over 52% reported they hide sanitary products when taking these to the toilet to prevent anyone else from being embarrassed, whilst 43% reported they felt people would make inappropriate remarks. The New York Post reported similar findings from a study commissioned by THINX, which indicated 58% of women felt embarrassed during the menstruation period whilst 42% experienced period-shaming, where 1 in 5 of those women reported these feelings were due to comments made by male friends[16].

It is evident that period poverty appears to be a global phenomenon, and key sociological as well as clinical features may differ due to varying risk factors in diverse geographical regions. To identify the impact of period poverty in diverse populations and common denominators observed between low-middle-income countries (LMICs) and high-income countries, it is vital to better understand current gaps in knowledge, policies and practice. Prior to this study, a comprehensive evidence synthesis had not been conducted to demonstrate the impact of period poverty. To achieve this, we developed the PLatform for the Analysis, Translation, and Organization of large-scale data project (PLATO) with the first component focusing on an evidence synthesis of the existing peer reviewed literature.

MATERIALS AND METHODS

A systematic methodology was developed and published as a protocol in PROSPERO (CRD-42022339536) to explore period poverty. A meta-analysis was conducted in addition to two key thematic variables identified through the systematic review of homelessness, infections, lived experiences and mental health impact due to menstruation.

Within the context of this study, rural and urban areas of the study were defined by natural administrative division of the location as reported within the peer review publications. The division of LMIC, middle-low-income countries (MICs) and high-income countries were defined based on the dividing standards of the World Banking Group.

The primary aim of this study was to provide a comprehensive understanding on period poverty, including outcomes associated menstruation such as affordability of menstrual products, disposable sanitary pads, accessibility to menstruation education tools, adequate menstrual hygiene management (MHM) practice and urinary tract infections. The difference in MHM practices in a variety of contexts such as age groups, religious beliefs, parents' educational status, and school absenteeism due to

dysmenorrhea were also explored.

Inclusion/exclusion

All observational and randomised clinical trials reporting menstruation challenges, menstrual poverty and menstrual products were included. Studies published in a peer review journal in English between the 30th of April 1980 and the 30th of April 2022 were included. All editorials, letters to editors and commentaries, and papers published in languages other than English were excluded.

Patient and public involvement

All the data used in this systematic review is publicly available. No further patient or public involvement was implemented for this paper.

Search strategy

Our search strategy included multiple electronic databases of PubMed, Web of Science, ScienceDirect, ProQuest and EMBASE. Subject index terms used were: Menstrual education, anthropology, period poverty, pads, sanitary pads, sanitary facilities, menstrual hygiene, urinary tract infections, menstrual health, and women's periods. The title and abstract of each publication were screened independently by two investigators. A consensus was reached for studies that were unsuitable for inclusion. Articles that were included were reviewed in in full independently by two investigators. These were re-reviewed independently prior to the data extraction. Difference of opinions and queries were resolved by the by the Principal Investigator and Chief Investigator.

Data extraction

We developed an extraction template specific to the objectives of the study although the aim was to gather a wider dataset to ensure vital data was not missed to answer the research aims comprehensively. Participants included in the study populations were those who live and/or are at risk of menstrual poverty. All studies reporting a menstrual product and/or an educational intervention associated with menstruation were extracted by way of the instruments, measures of tool and questionnaires. The final dataset was independently reviewed before the analysis commenced.

Participants included in the study populations were those who have experienced or are at risk of menstrual poverty. All studies reporting a menstrual product and/or an educational intervention associated with menstruation were extracted by way of the instruments, measures of tool and questionnaires. The final dataset was independently reviewed before the analysis commenced.

Risk of bias

The Newcastle-Ottawa Scale was used to assess the risk of bias (RoB) of the systematic included studies. A risk of bias table has been made available as a Supplementary material. The RoB table reflects a fixed set of biases linked to the study design, conduct and reporting (Table 1).

Meta-analyses

Out of the 1432 studies screened, 1182 were excluded. Of the 250 studies assessed for eligibility, 170 were excluded. Hence, 80 studies were systematically included, and 38 were included in the meta-analysis (Figure 1). The 38 studies were explored to obtain several indicators of period poverty, such as access to menstrual education tools, use of menstrual pads and MHM practice, as well as their related issues such as urinary tract infections, religious status, educational level of parents, geographical location including urban and rural areas, and the presence of a financial allowance.

To calculate the summary effect size across studies, meta-analysis of single proportions was applied to (a)-(c), and meta-analysis for comparison of two interventions was applied to (d)-(k)[17,18]. Since almost all outcomes of interest in the current analysis were dichotomous, meta-analysis with binary data was performed, and accordingly the pooled odds ratio (OR) with a 95% confidence interval (CI) was used to access the effect of two interventions[19,20]. Statistical heterogeneity was evaluated by the commonly used measure I^2 with P value, and further I^2 larger than 50% with a much small P value indicates strong heterogeneity. In comparison, I^2 less than 50% with a large P value indicates fairly weak heterogeneity[20]. In the presence of high heterogeneity, the random effects model was employed; instead, the fixed effects model was used if there was weak or no heterogeneity[21]. In some cases, subgroup analysis was carried out to identify the sources of heterogeneity, and sensitivity analysis was conducted for mainly assessing robustness of the synthesized results. Finally, publication bias was addressed seriously in the discussion part. All statistical outputs were reported using R[22,23].

A systematic analysis was used for studies that were excluded from the meta-analysis including those reporting lived experiences and the mental health impact associated with menstruation.

Table 1 Quality assessment of studies using a modified Newcastle-Ottowa scale

	Ref.	Selection				Comparability (**)	Outcome		Total (10*)
		Representativeness of the sample (*)	Sample size (*)	Non-respondents (*)	Ascertainment of exposure (**)		Assessment of outcome (**)	Statistical test (*)	
1	Garg *et al*[9], 2001	*	-	-	*	**	*	*	6*
2	Hennegan *et al* [44], 2016	*	-	-	*	**	*	*	6*
3	Sychareun *et al* [45], 2020	*	*	-	*	**	*	*	7*
4	Ha *et al*[46], 2020	*	*	-	*	**	*	*	7*
5	Fialkov *et al* [47], 2021	*	-	-	**	*	*	*	6*
6	Torondel *et al* [48], 2022	*	*	-	*	**	*	*	7*
7	Al-Jefout *et al* [49], 2015	-	-	-	*	**	*	*	5*
8	Birhane *et al* [50], 2019	*	*	-	*	**	*	*	7*
9	Alemayehu *et al*[51], 2020	*	*	-	*	**	*	*	7*
10	Kitesa *et al*[52], 2016	*	*	-	*	**	*	*	7*
11	Serbesa *et al* [53], 2018	*	*	*	*	**	*	*	8*
12	Shah *et al*[54], 2019	*	*	*	*	**	*	*	8*
13	Austrian *et al* [55], 2021	*	*	*	*	**	**	*	9*
14	Ocaktan *et al* [56], 2010	*	*	-	*	**	*	*	7*
15	Dhingra *et al* [57], 2009	*	*	-	*	**	**	*	7*
16	Boosey *et al* [58], 2014	*	-	-	*	*	**	*	6*
17	Amatya *et al* [59], 2018	*	*	-	*	*	**	*	7*
18	Caruso *et al* [60], 2020	*	*	*	*	**	*	*	8*
19	Sveinsdóttir *et al*[61], 2018	*	-	-	**	**	*	*	7*
20	Sveinsdóttir *et al*[62], 2017	*	*	-	**	**	*	*	8*
21	Mukherjee *et al* [63], 2020	*	*	-	*	**	*	*	7*
22	Hennegan *et al* [64], 2018	*	-	-	*	**	*	*	6*
23	Gharacheh *et al* [65], 2021	*	*	-	*	**	*	*	7*
24	Lee *et al*[66], 2017	*	-	-	*	**	*	*	6*
25	Hennegan *et al* [67], 2021	*	*	-	*	**	*	*	7*

26	Mao *et al*[68], 2021	*	*	-	*	**	*	*	7*
27	Roy *et al*[69], 2021	*	*	-	*	**	*	*	7*
28	Komada *et al* [70], 2019	-	-	-	**	**	*	*	6*
29	Crankshaw *et al*[71], 2020	*	*	-	*	**	*	*	7*
30	Afiaz *et al*[72], 2021	*	*	-	*	**	**	*	8*
31	Smith *et al*[73], 2020	*	-	-	*	**	*	*	6*
32	Toffol *et al*[74], 2014	*	*	*	**	**	**	*	10*
33	McMaster *et al* [75], 1997	*	-	-	*	*	*	*	5*
34	Janoowalla *et al*[26], 2020	*	-	-	*	**	**	*	7*
35	Ademas *et al* [76], 2020	*	*	-	*	**	*	*	7*
36	Bromberger *et al*[77], 2012	*	*	*	*	**	**	*	9*
37	Strine *et al*[78], 2005	*	*	-	*	**	*	*	7*
38	Mansoor *et al* [79], 2020	*	*	-	*	**	*	*	7*
39	Cardoso *et al* [80], 2019	*	-	-	*	**	*	*	6*
40	Choi *et al*[81], 2021	*	*	-	*	**	*	*	7*
41	Shimamoto *et al*[82], 2021	-	-	-	*	**	*	*	5*
42	Nohara *et al* [83], 2011	*	*	-	*	**	*	*	7*
43	Ahamed *et al* [84], 2015	*	*	-	-	**	*	*	6*
44	Mokhtari *et al* [85], 2020	*	*	-	*	**	*	*	7*
45	Warner *et al* [86], 2001	*	-	*	*	**	**	*	8*
46	Nishikitani *et al*[87], 2017	*	*	-	*	**	*	*	7*
47	Tanaka *et al* [88], 2013	*	*	-	*	**	*	*	7*
48	Zhou *et al*[89], 2010	*	-	-	*	**	**	*	7*
49	Chang *et al* [90], 2009	*	-	-	*	**	*	*	6*
50	Yirsaw *et al* [91], 2021	*	*	-	*	**	*	*	7*
51	Gokyildiz *et al* [92], 2013	*	-	-	*	**	*	*	6*
52	Jiang *et al*[93], 2019	*	*	-	*	**	*	*	7*
53	Parent *et al* [94], 2022	*	-	-	*	**	*	*	6*

54	Schoep *et al* [95], 2019	*	-	-	*	**	*	*	6*
55	Fernández-Martínez *et al* [96], 2020	*	*	-	*	**	**	*	8*
56	Abedian *et al* [97], 2011	-	*	-	**	**	*	*	7*
57	Beksinska *et al* [98], 2015	*	*	-	*	**	*	*	7*
58	Blake *et al*[99], 2018	*	*	-	*	**	*	*	7*
59	Djalalinia *et al* [100], 2012	*	*	-	*	**	*	*	7*
60	El-Mowafy *et al*[101], 2014	*	*	-	*	**	*	*	7*
61	Fakhri *et al* [102], 2012	*	-	-	*	**	*	*	6*
62	Montgomery *et al*[103], 2012	*	-	-	*	**	*	*	6*
63	Montgomery *et al*[44], 2016	*	*	*	*	**	*	*	8*
64	Hennegan *et al* [104], 2016	*	-	-	*	**	*	*	6*
65	Deshpande *et al*[105], 2018	*	*	-	*	**	*	*	7*
66	Cardoso *et al* [25], 2021	*	-	-	*	**	*	*	6*
67	Nyothach *et al* [106], 2015	*	-	-	*	**	**	*	7*
68	Kuhlmann *et al* [107], 2020	-	-	-	*	**	*	*	5*
69	Miiro *et al*[48], 2018	*	-	-	*	**	**	*	7*
70	Hensen *et al* [108], 2022	*	*	-	*	**	**	*	8*
71	Kuhlmann *et al* [109], 2019	*	-	-	*	**	**	*	7*
72	Shibeshi *et al* [110], 2021	*	*	-	*	**	**	*	8*
73	Kumbeni *et al* [111], 2020	*	*	-	*	**	**	*	8*
74	Adinma *et al* [112], 2014	*	*	-	*	*	*	*	6*
75	Eswi *et al*[113], 2012	*	-	-	*	**	*	*	6*
76	El-Hameed *et al*[114], 2011	*	-	-	*	**	*	*	6*
77	Abed *et al* [115], 2015	-	-	-	*	**	*	*	5*
78	Mohamed [116], 2012	*	-	-	*	**	*	*	6*
79	El-Mawgod *et al*[117], 2016	*	*	-	*	**	*	*	7*
80	Zegeye *et al* [118], 2009	*	*	-	*	**	*	*	7*

RESULTS

Studies with limited discussion about menstrual products, menstruation knowledge and MHM practice were excluded, resulting in a final dataset of 80 studies (Table 2). Of the 80 studies, 38 studies were selected for meta-analysis. Of 38 the studies, 34 were from LMICs and 4 from developed countries (non-LMICs).

Meta-analysis

Prevalence of using disposable sanitary pads: We explored the link of disposable sanitary pads as an indicator of period poverty. A meta-analysis of single proportions was applied to 32 studies with a sample of 212459 women, that indicated a prevalence of 45% (95%CI: 0.35-0.58). Figure 2A shows the forest plot for 32 studies. The value of 100% of I^2 (P value = 0) indicates a significant statistical heterogeneity.

To explore the sources of heterogeneity, a subgroup analysis was conducted using the geographical locations of the studies and demonstrated in a forest plot (Figure 2B). A statistically significant difference (P value < 0.01) was identified between LMICs and non-LMICs using sanitary pads where the pooled prevalence was 43% (95%CI: 0.33-0.56) and 76% (95%CI: 0.60-0.96), respectively. Figure 2B also showed that heterogeneity remained unchanged in LMICs (I^2 = 100%, P value = 0) and non-LMICs (I^2 = 98%, P value < 0.01), indicating that the identified heterogeneity was not geographical location influenced.

Prevalence of having knowledge/awareness on menstruation before menarche

Several surveys were meta-analysed to better understand adolescent girls' menstrual education and pre-menarche awareness. Common survey questions notably included, "*were you familiar with menstruation before you got your first period* [(Study 3)]", "*Information availability before reaching menarche* [(Study 4)]", "*heard about menstruation before menarche* [(Study 9)]", *and* "*prior knowledge about menstruation before menarche* [(Study 11)]" and "*awareness about menarche before its onset* [(Study 79)]". This information was used to conduct a meta-analysis of 11 studies with a sample size of 4944 young women. A high heterogeneity was detected with I^2 = 98% and P value < 0.01) (Figure 3A). The random effects model reported the overall prevalence to be 68% (95%CI: 0.56-0.82).

Prevalence of good MHM practice

Good MHM practice during menstruation is essential to prevent various other health issues such as urinary tract infections (UTIs)[24]. MHM practice lacks a standardised definition although a consensus is that it is expected that throughout the bleeding phase, people require clean absorbents, adequate frequency of absorbent change, washing the body with soap and water, adequate disposal, and privacy for managing menstruation. All involved studies predesigned some practice-related questions in research studies to determine the level of MHM practice, defined simply as good or bad. Figure 3B demonstrates a forest plot of the prevalence of good MHM practice across ten studies with a total of 5432 women. The random effects model was used due to strong heterogeneity indicated by I^2 = 99% and P value < 0.01. The overall prevalence of good MHM practice was 39% (95%CI: 0.25-0.61).

Rural-urban difference in MHM practice level (good/bad)

A total of 5 studies with a sample size of 2705 women reported differences of MHM practice levels within rural and urban settings. The pooled OR of good MHM practice between rural and urban areas was 0.30 (95%CI: 0.13-0.69), indicating that women living in rural area were 0.70 times less likely to have good MHM practices in comparison to those living in an urban area. A high heterogeneity of 91% of I^2 (P value < 0.01) was identified (Figure 3C), possibly due to the differences in covariates, assessment tools and other factors.

Difference of MHM practice level (good/bad) between two age groups

Based on available data from 3 studies with a total of 1637 adolescent girls, special attention is paid to two groups aged at less than or equal to 15 years and 16 to 19 years. The random effects model yielded a I^2 of 82% with a pooled OR of good MHM practices between two age groups of 0.77 (95%CI: 0.44-1.34), which is not statistically significant (Figure 4A).

Difference of MHM practice level (good/bad) among adolescent girls with uneducated and educated father/mother

Parents' educational background showed an impact on MHM practices among adolescent girls. In some studies father's or mother's educational status was divided into illiterate and literate, while in other studies categorised as uneducated, primary education, secondary or high school education, and college or above. To simplify the data, father's or mother's educational status was defined as uneducated, where either parent lacked primary education whilst, educated was anyone that had any above secondary. Figure 4B showed a forest plot for difference of MHM practice level (good/bad) among

Table 2 Characteristics of the studies included in the systematic review

Study ID	Ref.	Year	Study type	Sample size	Country	Mean age	Meta-analysis inclusion Y/N
1	Garg *et al*[9]	2001	Epidemiological and sociological study	380	India		Y
2	Hennegan *et al*[44]	2016	Cross-sectional study	201	Uganda	14.2	Y
3	Sychareun *et al*[45]	2020	Cross-sectional study	343	LAO	15.6	Y
4	Ha *et al*[46]	2020	Cross-sectional study design with systematic random sampling	589	Bangladesh	15.5	Y
5	Fialkov *et al*[47]	2021	Pre- and post-test design that compared six cohort groups	311	Kenya		N
6	Torondel *et al*[48]	2022	Nested within a pair-matched cohort study	1045	India	27	Y
7	Al-Jefout *et al*[49]	2015	Cross-sectional study	272	Jordanian	22	Y
8	Birhane *et al*[50]	2019	Cross-sectional study	466	Ethiopia	15.5	Y
9	Alemayehu *et al*[51]	2020	Cross-sectional study	301	Ethiopia	15.87	Y
10	Kitesa *et al*[52]	2016	Cross-sectional study	430	Ethiopia	16	Y
11	Serbesa *et al*[53]	2018	Cross-sectional study	310	Ethiopia	15.72	Y
12	Shah *et al*[54]	2019	Cross-sectional study	331	Gambia	15.3	Y
13	Austrian *et al*[55]	2021	Cluster RCT	3489	Kenya	14.8	N
14	Ocaktan *et al*[56]	2010	Cross-sectional study	400	Turkey	32.19	Y
15	Dhingra *et al*[57]	2009	Cross-sectional study	200	India	13.97	Y
16	Boosey *et al*[58]	2014	Cross-sectional study	140	Uganda	14.45	N
17	Amatya *et al*[59]	2018	Cross-sectional mixed-methods study	104	Nepal	15	N
18	Caruso *et al*[60]	2020	Cross-sectional study	878	India	26.8	Y
19	Sveinsdóttir *et al*[61]	2018	Cross-sectional study	319	Iceland	30	Y
20	Sveinsdóttir *et al*[62]	2017	Cross-sectional study	319	Iceland	30	N
21	Mukherjee *et al*[63]	2020	Cross-sectional study	1342	Nepal		N
22	Hennegan *et al*[64]	2018	Cross-sectional study	2934	Nigeria	26.66	Y
23	Gharacheh *et al*[65]	2021	Cross-sectional study	515	Iran	29.61	N
24	Lee *et al*[66]	2017	Prospective observational cohort study	1495	USA	46.8	N
25	Hennegan *et al*[67]	2021	Secondary data analysis	11806	Burkina Faso, Niger, Nigeria		N
26	Mao *et al*[68]	2021	Cross-sectional study	156055	China	26.32	N
27	Roy *et al*[69]	2021	Secondary data analysis	94034	India		Y
28	Komada *et al*[70]	2019	Cross-sectional study	150	Japan	18.8	N
29	Crankshaw *et al*[71]	2020	Mixed-method study	472	South Africa	17.5	Y
30	Afiaz *et al*[72]	2021	Cross-sectional study	54242	Bangladesh	29	Y
31	Smith *et al*[73]	2020	Secondary data analysis	38257	Uganda, Kenya, Ethiopia *etc.*		Y
32	Toffol *et al*[74]	2014	Cross-sectional study	4391	Finland	56.2	N
33	McMaster *et al*[75]	1997	exploratory phase of the study	50	Zimbabwe		N
34	Janoowalla *et al*[26]	2020	Prospective cohort study	240	Rwanda	19.1	Y
35	Ademas *et al*[76]	2020	Cross-sectional study	602	Ethiopia		Y
36	Bromberger *et al*[77]	2012	Multisite study	934	USA		N
37	Strine *et al*[78]	2005	Cross-sectional study	11648	USA		N

38	Mansoor *et al*[79]	2020	Cross-sectional study	1777	Pakistan	20.38	Y
39	Cardoso *et al*[80]	2019	Baseline data from a larger RCT	1800	Nepal	34.5	N
40	Choi *et al*[81]	2021	Cross-sectional study	8658	Korea	35.1	Y
41	Shimamoto *et al*[82]	2021	Self-reporting questionnaire survey	6048	Japan		N
42	Nohara *et al*[83]	2011	Cross-sectional study	2166	Japan		N
43	Ahamed *et al*[84]	2015	Cross-sectional study	344	India	28	Y
44	Mokhtari *et al*[85]	2020	Cross-sectional study	164	Iran	27.78	N
45	Warner *et al*[86]	2001	Cross-sectional study	952	Scotland		N
46	Nishikitani *et al*[87]	2017	Cross-sectional study	505	Japan		N
47	Tanaka *et al*[88]	2013	Online survey	19254	Japan	33.6	N
48	Zhou *et al*[89]	2010	Cross-sectional study	1642	China	37	N
49	Chang *et al*[90]	2009	Cross-sectional survey	1095	Taiwan		N
50	Yirsaw *et al*[91]	2021	Cross-sectional study	713	Ethiopia	21.13	N
51	Gokyildiz *et al*[92]	2013	Case-control study	295	Turkey		N
52	Jiang *et al*[93]	2019	Cross-sectional study	12881	China		N
53	Parent *et al*[94]	2022	Cross-sectional study	1153	France	31.7	Y
54	Schoep *et al*[95]	2019	Cross-sectional study	42879	Netherlands	28.7	N
55	Fernández-Martínez *et al*[96]	2020	Cross-sectional study	7208	Spain	19.51	N
56	Abedian *et al*[97]	2011	RCT	165	Iran		N
57	Beksinska *et al*[98]	2015	Randomized two-period Cross-over trial	124	South Africa	29	N
58	Blake *et al*[99]	2018	Mixed-methods evaluation	636	Ethiopia	13.45	Y
59	Djalalinia *et al*[100]	2012	Community-based participatory research	1823	Iran		N
60	El-Mowafy *et al*[101]	2014	Quasi-experimental study	234	Egypt		N
61	Fakhri *et al*[102]	2012	Quasi-experimental study	698	Iran	15.7	N
62	Montgomery *et al*[103]	2012	Non-randomized trial	120	Ghana	15.7	N
63	Montgomery *et al*[44]	2016	Cluster quasi-randomised controlled trial	1124	Uganda		N
64	Hennegan *et al*[104]	2016	Secondary data analysis	205	Uganda	14.2	Y
65	Deshpande *et al*[105]	2018	Cross-sectional study	100	India		Y
66	Cardoso *et al*[25]	2021	Online survey	471	United States	20.6	N
67	Nyothach *et al*[106]	2015	Retrospective study		Kenya		N
68	Kuhlmann *et al*[107]	2020	Cross-sectional study	58	USA	15.21	N
69	Miiro *et al*[48]	2018	Cross-sectional study	352	Uganda	15.6	Y
70	Hensen *et al*[108]	2022	Mixed-methods analysis	7546	Zambia		N
71	Kuhlmann *et al*[109]	2019	Cross-sectional study	183	USA	35.8	Y
72	Shibeshi *et al*[110]	2021	Cross-sectional study	1078	Ethiopia	17.35	Y
73	Kumbeni *et al*[111]	2020	Cross-sectional study	705	Ghana		Y
74	Adinma *et al*[112]	2014	Cross-sectional study	550	Nigeria		Y
75	Eswi *et al*[113]	2012	Cross-sectional study	200	Egypt	15.45	N
76	El-Hameed *et al*[114]	2011	Cross-sectional study	160	Egypt	17.2	N
77	Abed *et al*[115]	2015	Cross-sectional study	100	Egypt	14.25	Y
78	Mohamed[116]	2012	Cross-sectional study	885	Egypt	16	Y
79	El-Mawgod *et al*[117]	2016	Cross-sectional study	344	Saudi Arabia	16.2	Y

80	Zegeye *et al*[118]	2009	Cross-sectional study	612	Ethiopia	16.9	Y

RCT: Randomized control trial.

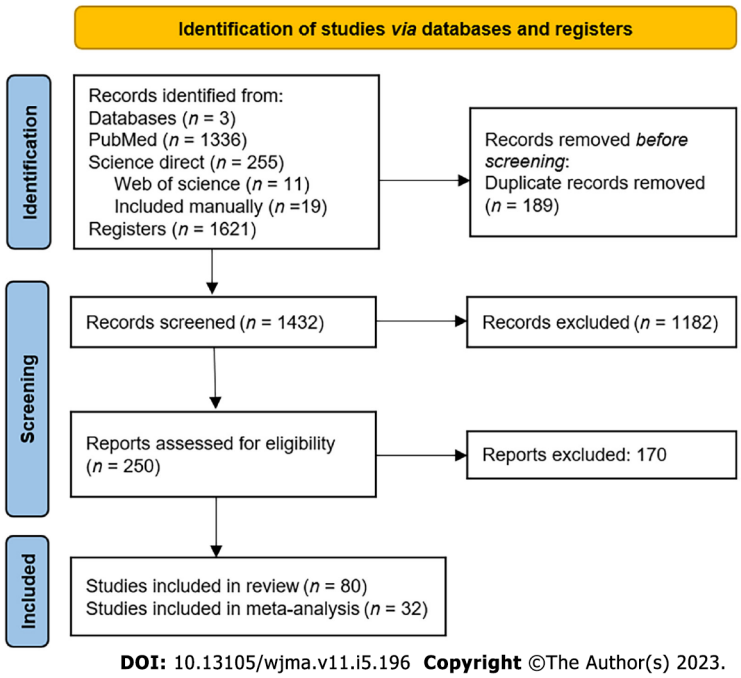

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Figure 1 PRISMA 2020 flow diagram showing study selection.

adolescent girls with uneducated and educated fathers, and the pooled OR was 0.55 (95%CI: 0.36-0.83). This provides significant evidence of the lower prevalence of good MHM practice among adolescent girls with uneducated fathers. Similarly, Figure 4C demonstrated that adolescent girls with uneducated mothers were 0.48 times less likely to have good MHM practices than those with educated mothers.

Difference of MHM practice level (good/bad) among adolescent girls without and with pocket money

To some extent, the possibility of getting a financial allowance, also referred to as a pocket money indicated the socioeconomic status of the family which would indicate their affordability to disposable sanitary pads. Thus, two studies that reported on the use of disposable sanitary pads with a total of 731 adolescent girls were analysed. The forest plot (Figure 5A) demonstrates the difference of MHM practice levels among adolescent girls with and without pocket money. The I^2 = 0 (P value = 0.41) means that there was very weak statistical heterogeneity. The pooled OR was 0.45 (95%CI: 0.32-0.64), indicating that adolescent girls who have no pocket money were 0.55 times less likely to have good MHM practices than those who have pocket money.

Difference of MHM practice level (good/bad) among adolescent girls of having no and having discussion about menstruation with parents

Discussion points between a parent and a young girl were explored where the paradigm indicated open discussions around menstruation issues. Responses to these questions reflects the parent-child relationship. The forest plot indicates (Figure 5B) a difference between MHM practices among adolescent girls who did not have a discussion with their parents *vs* those who had a discussion was 0.46 (95%CI: 0.28-0.75).

Difference of MHM practice level (good/bad) among female followers of different religions

Literature indicated the presence of a correlation between religious views and MHM practices, as demonstrated within 3 studies conducted in Ethiopia, with a combined sample size of 1128 adolescent girls. Thus, a pairwise meta-analysis was employed to compare the MHM practice levels among women of Orthodox, Protestant and Islamic beliefs. Figures 5C-E demonstrated forest plots comparing Orthodox *vs* Protestant, Protestant *vs* Islam, and Orthodox *vs* Islam, respectively. The corresponding pooled ORs were 1.81 (95%CI: 0.47-6.99), 0.66 (95%CI: 0.23-1.92), and 0.66 (95%CI: 0.87-1.72). Based on the CIs, there is no statistically significant difference in MHM practice levels among women from Orthodox, Protestant and Islamic beliefs.

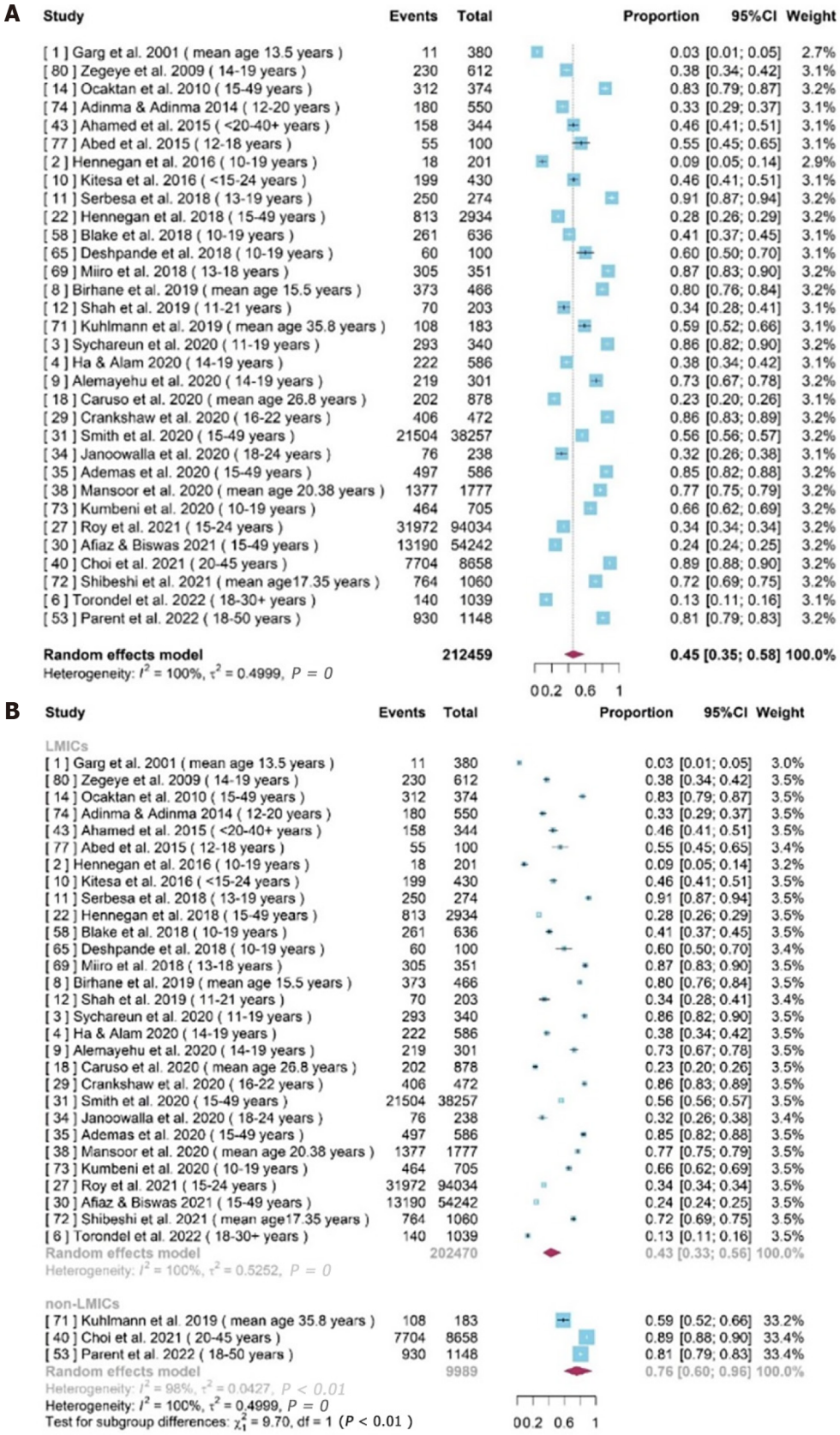

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Figure 2 Forest plots showing the prevalence of using disposable sanitary pads. A: Forest plot shows the prevalence of using disposable sanitary pads across 32 studies; B: Forest plot shows the prevalence of using disposable sanitary pads in low-middle-income countries (LMICs) and non-LMICs, respectively.

School absenteeism due to dysmenorrhea

Dysmenorrhea is another key feature of menstruation indicating an important reason for school absenteeism among adolescent girls. Two studies reported mild and moderate menstrual pain among

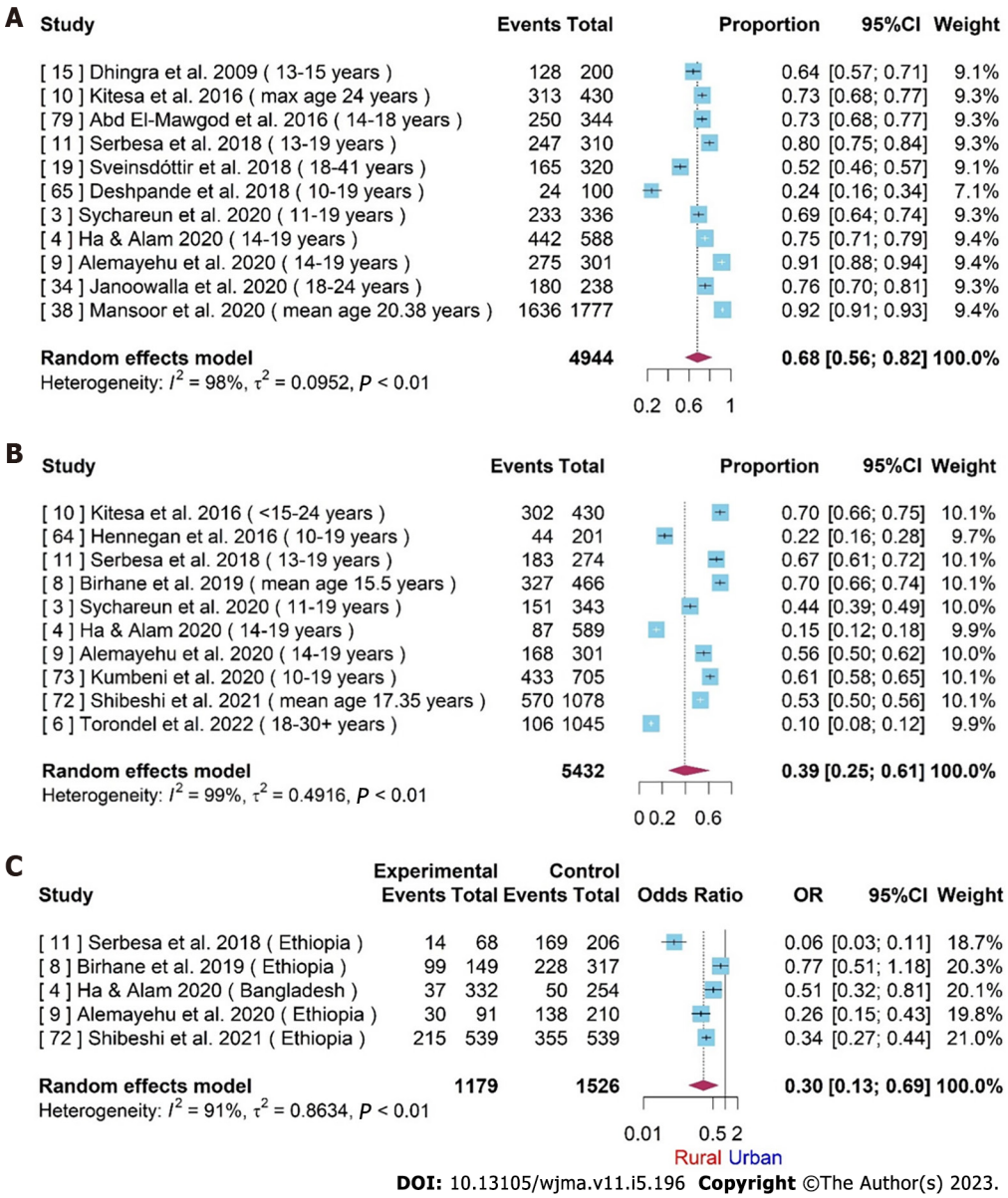

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Figure 3 Forest plots exploring menstrual education and hygiene management practices. A: Forest plot for the prevalence of having knowledge/awareness on menstruation before menarche across 11 studies; B: Forest plot for the prevalence of good menstrual hygiene management (MHM) practice across ten studies; C: Forest plot for the rural-urban difference of MHM practice level (good/bad).

their participants. We combined mild to moderate pain and defined as not severe menstrual pain for the analyses. This was combined with four studies. The total sample size was 1582 (Supplementary Figure 1). The pooled OR of school absenteeism between adolescent girls with severe and not severe menstrual pain was 4.26 (95%CI: 2.27-7.99), indicating those with severe menstrual pain were 4.26 times more likely to miss school than those without menstrual pain.

Participants in study 7 were aged between 19 to 25 years of age, whilst others were less than 19 years old. There appears to be high heterogeneity (I^2 =83%, P value < 0.01) in the sample. Thus, it was excluded, and the heterogeneity was re-evaluated where the pooled OR is 2.98 (95%CI: 2.29-3.87). Supplementary Figure 2 indicates I^2 to be 0 with a P value of < 0.01. The heterogeneity, therefore, was specific to Study 7. The participant group of 19 to 25 years old, or, more precisely, age group may be one of the main sources of heterogeneity.

To explore the association between school absenteeism and whether or not using disposable sanitary pads have any impact, a meta-analysis was applied to 3 studies with a total sample size of 1280 adolescent girls. Supplementary Figure 3 indicated significant evidence of statistical heterogeneity (I^2 =83%, P value < 0.01). The pooled OR of 2.08 (95%CI: 1.10-3.91) indicates that adolescent schoolgirls who did not use disposable sanitary pads were 1.08 times more likely to be absent from school than those using sanitary pads.

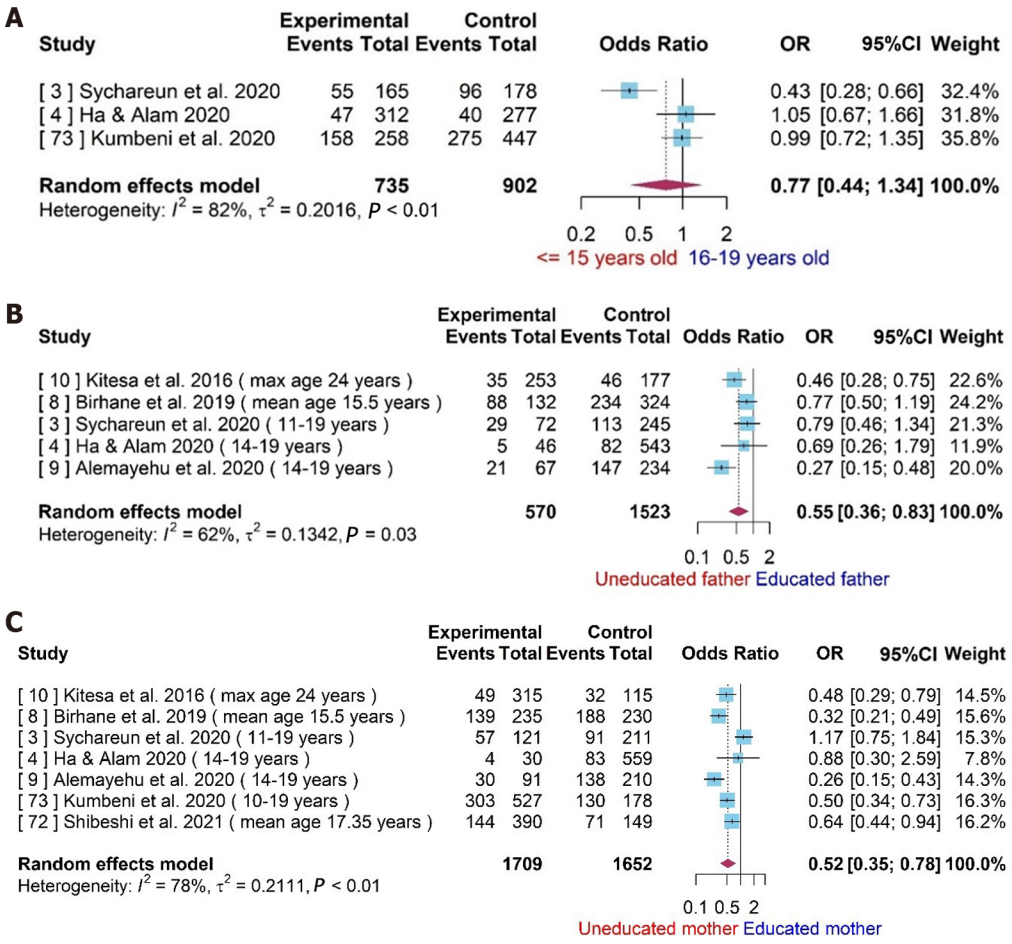

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Figure 4 Forest plot for the difference of menstrual hygiene management. A: Forest plot for the difference of menstrual hygiene management (MHM) practice level (good/bad) between two age groups; B: Forest plot for difference of MHM practice level (good/bad) among adolescent girls with uneducated and educated father; C: Forest plot for difference of MHM practice level (good/bad) among adolescent girls with uneducated and educated mother. Available in Supplemental material.

Association between dysmenorrhea and regularity of menstrual cycle

As presented in the former part, there is a statistically significant association between the severity of dysmenorrhea and school absenteeism. To further identify the possible causes of dysmenorrhea, two studies were meta-analysed with a total sample size of 1285 with confirmed experience of regular or irregular menstrual cycles. Supplementary Figure 4 indicated a lack of statistical heterogeneity (I^2 = 0, P value = 0.89) and thus the fixed effects model was used. The pooled OR was 2.31 (95%CI: 1.76-3.02), indicating the prevalence of dysmenorrhea among adolescent girls with irregular menstrual cycles is 2.31 times as high as those with a regular cycle.

Another key area of period poverty is the associated mental health impact, which can differ between those who suffer from mental illness and those who do not. Whilst there was insufficient data for a meta-analysis, there was evidence to suggest a link between menstruation and prevalence of stress, anxiety, and depression[3]. In addition, socioeconomic status can impact the prevalence of stress, anxiety and depression experienced by different populations.

DISCUSSION

Period poverty is a global health issue, more prominent in low-middle-income countries. There are varying risk factors dependent on geographical location and this reflects in the differing sociological and clinical features, as explored in this paper.

This study demonstrates correlations between severity of dysmenorrhea and school absenteeism among girls between 14-19 years of age with and without regular menstruation. Another key area of period poverty is the associated mental health impact, which can differ between those who suffer from mental illness and those who do not. Whilst there was insufficient data for a meta-analysis, there was evidence to suggest a link between menstruation and prevalence of stress, anxiety, and depression[3]. In

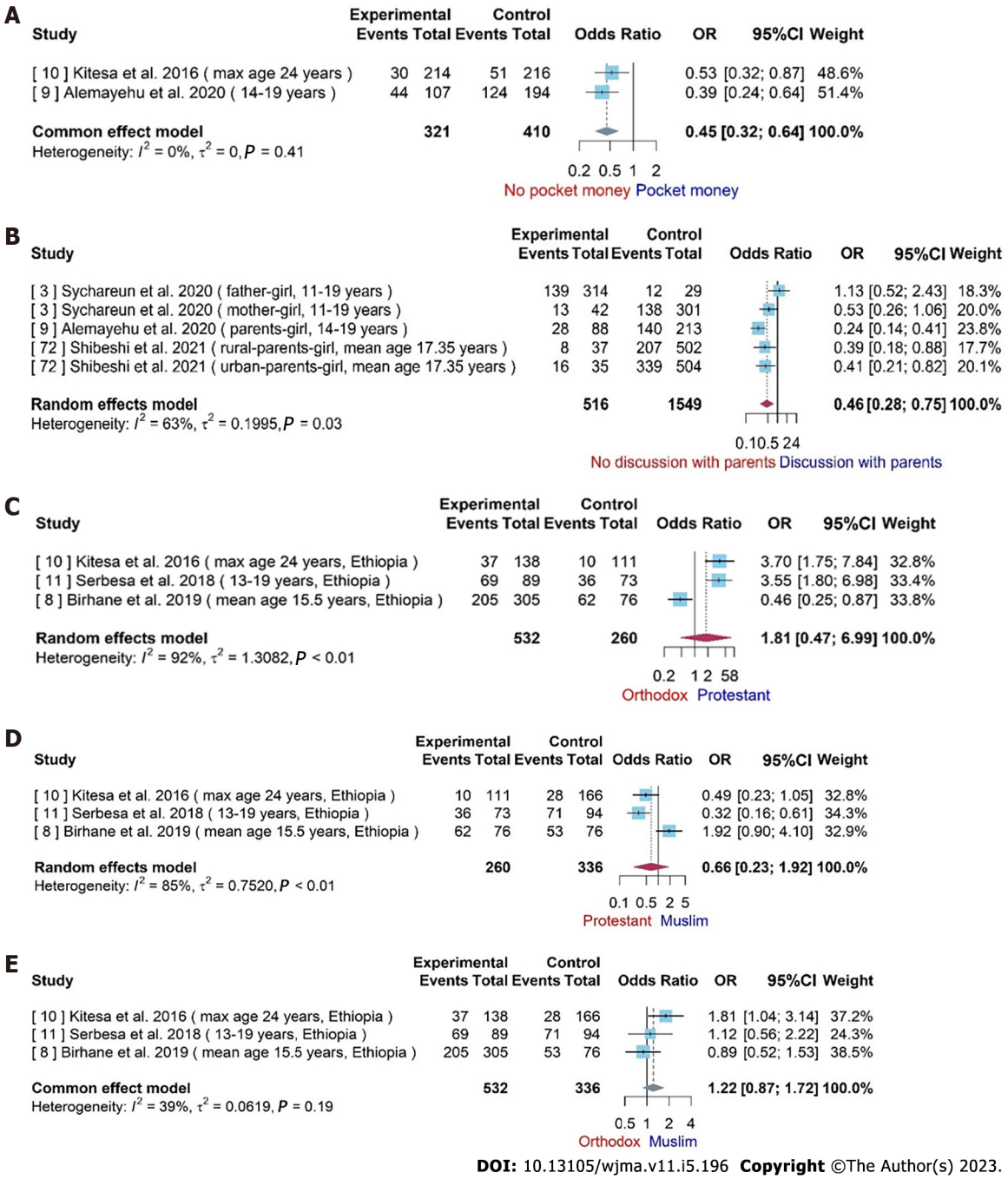

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Figure 5 Forest plots showing the differences in menstrual hygiene management across various factors. A: Forest plot for difference of menstrual hygiene management (MHM) practice level (good/bad) among adolescent girls without and with pocket money; B: Forest plot for difference of MHM practice level (good/bad) among adolescent girls of having no and having discussion about menstruation with parents. Available in Supplementary material; C: Forest plot for the difference of MHM practice level (good/bad) among adolescent girls with orthodox and protestant; D: Forest plot for difference of MHM practice level (good/bad) among adolescent girls with protestant and Muslim. Available in Supplementary material; E: Forest plot for difference of MHM practice level (good/bad) among adolescent girls with orthodox and Muslim. Available in Supplemental material.

addition, socioeconomic status can impact the prevalence of stress, anxiety and depression experienced by different populations. This could be exacerbated among those acquiring UTIs[24,25].

UTIs have been reported by Das and colleagues to be a common problem among those without pad use. Janoowalla and colleagues demonstrated no change in the prevalence of urinary tract infections between those using and not-using pads in the Kibogora region in Rwanda[26]. Das and colleagues indicated a higher risk of urogenital infections among women using reusable absorbent pads within the Odisha region in India[24]. Bacterial vaginosis (BV) is another issue impacting women with poorer menstrual practices. Das and colleagues reported that menstrual hygiene practices were associated with a symptomatic BV or UTI[24].

MHM practices were another key endpoint in this study which demonstrated to differ among women of Islamic, Protestant and Orthodox religious beliefs in Ethiopia. Representativeness of these findings to other ethnicities requires further research.

Homelessness is another facet that is vital to explore to identify the impact of period poverty. For example, in the United States, 553000 experience homelessness in a night compared to 32000 in the UK [27,28]. It is reported that 25% of homeless service users in the UK are single women and 28% in the United States. These could be underestimated as hidden homeless is another facet where people do not access services but stay in temporary accommodation settings, including friends and relatives. Many official reports lack information regarding experiences of menstruation among the homeless. Padgett and colleagues demonstrate that this multifaceted concern or as a feature of reproductive health is now being explored, although comprehensive evidence is required[29]. Phenomenology demonstrates homeless menstrual lived experiences, which is an important aspect of understanding period poverty by exploring the interrelatedness between the consciousness, body, and the flesh of a woman[30]. Homeless people are a marginalised community; thus, menstruation could emphasize their vulnerability. Historically, social sciences research has focused on commodification, medicalisation and stigma associated with menstruation. Anglo-American publications have also failed to discuss intersectionality and focus primarily on white, middle-class, cisgender women or in a developmental context where women are in poverty[31-34]. The sociopsychological and socioeconomic aspects associated with women living in poverty *vs* those not can sometimes be polarised from a period poverty perspective. Health outcomes among disenfranchised groups of women due to lack of or minimal access to menstrual products can have significant effects where clinical interventions would be required to manage the symptoms, including systemic issues. Another facet is that the supply of menstrual products to homeless services such as shelters, and day centers should be more effective. This should include the availability of staff that could be approached to talk about menstruation or any associated problems[35].

Another facet of period poverty is the composition of menstrual pads which is not the same in terms of their textile and polymer composition. Varying viscosity of menstrual flow could also impact the suitability of the differing pads, given that these are worn for different periods. Another aspect to consider as an external factor for menstrual products would be to produce material that can be disposed of in a biodegradable manner. Velasco Perez *et al*[36] and Hait *et al*[37] indicated that sanitary pads have a higher negative environmental footprint due to eutrophication and climate change. Limited evidence is available about menstrual underwear and menstrual cups associated with environmental impact. This further complicates menstrual hygiene issues, equitable availability, and acceptability, especially among LMIC populations.

Whilst this study has indicated the majority of the evidence on period poverty is within LMIC and MICs, there appears to be a lack of studies available within developed countries despite the definition of "period poverty", including the inability to afford menstrual products. Given the risk of living costs, many media publications and social media posts indicate that period poverty is a concern within developed countries. For example, Cardoso and colleagues indicated that women in the United States reported 14.2% experienced period poverty in 2020, with an additional 10% experiencing it monthly [25]. Whilst knowledge, attitude and practices associated with menstruation among poorer and vulnerable communities are likely to be lower regardless of the geographical location. As a result, the psychosocial dynamics may have a negative impact. The findings of these studies may have been exacerbated due to the coronavirus disease 2019 pandemic with substantial increases in unemployment and cost of living. Basic goods and service cost increase includes those of menstrual products. Thus, the pandemic has had gendered implications impacting the vulnerability of women. Caretaker roles of women have significantly grown as a result of lockdowns, and such requirements have been inadequately explored[38].

In addition, limited evidence is demonstrated around mental health implications due to the period of poverty. Cardoso and colleagues demonstrated an association between period poverty and depression among women within the United States who were previously depression naïve[25]. This is similar to the findings reported between food insecurity associated with depression in adults and anxiety, depression and suicidal ideation among adolescents[25,39-41]. Similarly, depression and anxiety were reported among people experiencing housing insecurities compared to those with stable houses[42,43].

The data identified is limited to either smaller sample sizes and/or geographical locations that could limit the generalisability of the findings to introduce impactful and meaningful changes to policy and clinical practice

CONCLUSION

Period poverty is an international issue, varying based on geographical locations, social implications, and economical factors. Better understandings of this problem will highlight current gaps in knowledge, policies, and practice. Undoubtedly, many issues affect the experiences of managing menstruation and access to menstrual products. To address the current gaps and ensure period poverty can be minimised,

comprehensive research would be required. Policymakers and independent authorities should consider improved healthcare legislation, equitable access to menstrual products, information, and healthcare providers.

ARTICLE HIGHLIGHTS

Research background

Period poverty is an international health concern, impacting thousands of women and girls, especially those in underdeveloped regions or those struck with conflict and disaster. Due to issues with menstrual education and access to menstrual hygiene products, many females compromise their daily routines (*e.g.*, not attending school or going to work). There is a lack of a comprehensive evidence synthesis in relation to period poverty hence the PLatform for the Analysis, Translation, and Organization of large-scale data project (PLATO) was developed with this systematic review and meta-analysis as the first stage.

Research motivation

Period poverty influences various health and social factors to varying degrees, dependent on the geographic location and other risk factors – this effect is amplified in low- and middle- income countries. To better understand the impact of period poverty, research exploring and highlighting current gaps in knowledge in key. Following this, improved legislation and policies for women and girls will enable better access to menstrual hygiene products and accurate menstrual education.

Research objectives

Due to the sheer lack in period poverty research, especially in low- and middle- income countries, this systematic review and meta-analysis aimed to explore current understandings and highlight any areas for future research. The primary outcomes included factors associated to menstrual hygiene products, such as accessibility and affordability, but also menstrual hygiene management and education. Variations in relation to age, location, religion, and parental and individual education was also explored.

Research methods

A systematic review and meta-analysis were conducted to explore period poverty with all related observational and randomised clinical trials included in this report. Studies published in English, between the 30th of April 1980 and the 30th of April 2022 were included. An extraction template was specifically developed in line with the objectives of the study to ensure that research aims were addressed comprehensively.

Research results

Overall, 80 studies were included in the systematic review and 38 in the meta-analysis and various statistically significant findings were uncovered. Sanitary pads were used a lot more in non-Low- and Middle-income countries, with women in rural areas being 0.7 times less likely to have good menstrual hygiene and management practices. School girls who reported irregular menstrual cycles experienced severe menstrual pain and those with severe pain were almost 5 times more like to miss out on school.

Research conclusions

This study demonstrates correlations between severity of dysmenorrhea and school absenteeism among girls with and without regular menstruation. It also explored how period poverty is the associated mental health impact, with evidence to suggest a link between menstruation and prevalence of stress, anxiety, and depression. This study has indicated that the majority of the evidence on period poverty is within low-middle-income countries and middle-low-income countries. It is possible that the findings of this study could have been exacerbated due to the coronavirus disease 2019 pandemic.

Research perspectives

Period poverty is an under-researched area despite is being a global social and health issue. This research has outlined current understandings of period poverty but also where the gaps lie. Following on from this, policies and practices can be introduced and developed to ensure women and girls are supported across the globe in relation to menstrual products, information, and healthcare providers.

FOOTNOTES

Author contributions: Delanerolle G conceptualised the PLATO project as part of the ELEMI program which includes

three work-packages; Delanerolle G, Cavalini H, Shi JQ and Phiri P developed the systematic review protocol and embedded this within the PLATO project's work package 1; Delanerolle G and Shi JQ designed the statistical analysis plan; Yang XJ, Delanerolle G, and Shi JQ completed the analysis; Sajid S and Phiri P completed the risk of bias and Newcastle-Ottawa Scale; All authors critically appraised and commented on previous versions of the manuscript; All authors read and approved the final manuscript.

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META-ANALYSIS

Vitamin D deficiency among outpatients and hospitalized patients with diabetic foot ulcers: A systematic review and meta-analysis

Hyder Osman Mirghani

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Abstract

BACKGROUND

The definition of diabetic foot syndrome (DFS) varies depending on the location and resources. Few classifications are available according to the indication. DF ulcers and vitamin D deficiency are common diseases among patients with diabetes. Previous literature has shown an association between DF ulcer (DFU) and vitamin D deficiency. However, the available meta-0analysis was limited by substantial bias.

AIM

To investigate the association between DFUs and vitamin D levels.

METHODS

We searched PubMed, MEDLINE, and Cochrane Library, EBSCO, and Google Scholar for studies comparing vitamin D levels and DF. The keywords DFU, DFS, diabetic septic foot, vitamin D level, 25-hydroxy vitamin D, vitamin D status, and vitamin D deficiency were used. The search engine was set for articles published during the period from inception to October 2022. A predetermined table was used to collect the study information.

RESULTS

Vitamin D level was lower among patients with DFU compared to their counterparts [odds ratio (OR): -5.77; 95% confidence interval (CI): -7.87 to -3.66; χ^2 was 84.62, mean difference, 9; I^2 for heterogeneity, 89%; $P < 0.001$ and P for overall effect < 0.001]. The results remained robust for hospitalized patients (OR: -6.32 95%CI: -11.66 to -0.97; χ^2 was 19.39; mean difference, 2; I^2 for heterogeneity, 90%; $P = 0.02$).

CONCLUSION

Vitamin D was lower among outpatients and hospitalized patients with DFUs. Further larger randomized controlled trials are needed.

Key Words: Vitamin D deficiency; Diabetic foot ulcer; Outpatient; Hospitalized patients; Diabetic foot syndrome

Core Tip: This is the first study to assess the relationship between diabetic foot ulcer and vitamin D deficiency, avoiding the bias of the two published meta-analyses.

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INTRODUCTION

Diabetes mellitus (DM) is an epidemic globally. DM is a morbid disease with many complications including microvascular and microvascular disease. Diabetic foot syndrome (DFS) is defined as peripheral neuropathy, limited joint mobility, peripheral arterial disease, immunopathy, ulceration, and Charcot arthropathy[1]. The combination of FS elements provides an environment for unrecognized injury, foot infection, and possible amputation[2]. DFS is characterized by peripheral arterial disease, but the symptoms are masked by the accompanying peripheral neuropathy. The pathology varies from pre-ulcerative callouses, ulceration, and necrosis developing at the site of high pressure (deformities of the toes and feet). Patient education and feet inspection are mandatory because repetitive trauma might pass unnoticed due to the loss of pain sensation[3]. DFS is a common complication of diabetes with a great economic burden; DTS substantially affects the patient's quality of life and leads to premature death. In addition, patients with DFS are prone to psychiatric disease[4].

There are nearly 40 classifications for DFS, with wide variation depending on the availability of resources and geographical variations. It is recommended to use classification in light of specific indications. Few classifications have been validated for use; the site, ischemia, neuropathy, bacterial infection, area, and depth (SINBAD) is six questions with yes or no answers with a maximum of six points. SINBAD score is better for communication between clinicians[5]. While, the Infectious Diseases Society of America/International Working Group on Diabetic Foot, and wound depth, ischemia, and foot infection scoring are better for infection and perfusion respectively[6,7]. The spectrum of DFS varies from minor erythema to tissue necrosis and lower limb deformity and amputation [8]. The mortality of DFS is comparable to breast and lung cancer. Five-year mortality for minor and major amputations, Charcot, and DF ulcer (DFU) were 56.6%, 46.2%, 30.5%, 29%, respectively. The pooled mortality from breast, all cancer, and lung cancer were 9%, 30%, and 80% respectively[9].

The lifetime of developing FUs among patients with diabetes varies between 19% and 34% with nearly two-thirds of recurrence in 5 years, and 1 in 5 patients with moderate to severe FUs resulting in amputation. The majority of lower extremities amputations are preceded by FUs and three amputations occur every minute due to diabetes. Patients with FUs had a 2.5 times mortality rate compared to their counterparts[10,11].

25-hydroxyvitamin D (25(OH)D) is present in almost all immune cells and is a major immunomodulatory hormone. In addition, the vitamin is a potent endothelial membrane stabilizer[12]. Due to its anti-inflammatory effects, the active form of vitamin D plays an important role in inflammatory diseases including rheumatic disorders, and a growing piece of evidence is present regarding its effects on infectious diseases[13]. Vitamin D deficiency is common; larger studies suggest that in Europe, 40% and 13% of the population are vitamin D-deficient and severely deficient, respectively[14]. Vitamin D deficiency is associated with vascular diseases including DM, hypertension, and dyslipidemias[15].

The small number of included studies, including studies published by the same authors and including poster presentations[16,17], limits the previous meta-analysis on vitamin D deficiency and diabetic septic foot. Therefore, this meta-analysis investigated vitamin D levels among patients with the diabetic septic foot.

MATERIALS AND METHODS

Eligibility criteria

The studies were eligible if they compared the level of vitamin D among patients with DFU and their counterparts without DFUs and they are randomized controlled trials or case-control studies, prospective and retrospective cohorts, and cross-sectional studies. Case reports, case series, and animal and experimental studies were excluded.

Outcomes measures

The primary outcome was the level of vitamin D among patients with DFUs.

Vitamin D assessment methods

Vitamin D measurement varied between the included studies. References 18, 19, 21, and 23 used the enzyme-linked immunosorbent assay; references 20, 22, and 25 used radioimmunoassays; references 24, 26, and 28 used the electrochemiluminescence immunoassay; reference 27 used liquid chromatography-tandem mass spectrometry; and reference 29 used the chemiluminescence assay.

Setting and DFU definition

All of the studies used outpatients except 18, 24, 28, and 29, in which hospitalized patients were included.

Information sources and search

The researcher searched PubMed, MEDLINE, and Cochrane Library, EBSCO, and Google Scholar using the keywords DFU, DFS, diabetic septic foot, vitamin D level, 25-hydroxy vitamin D, vitamin D status, and vitamin D deficiency. The search engine was set for articles published during the period from inception to October 2022. A predetermined table was used to collect study information including author name, year of publication, country, age, sex, patient's number in the control and interventional groups, duration of diabetes, hemoglobin A1c (HbA1c) in the intervention and control groups, vitamin D level among patients with FUs and control groups (Figure 1 and Tables 1-3).

Data analysis

The RevMan (version 5.4) system for meta-analysis was used, and the data were all continuous. We pooled data from 12 studies to compare vitamin D levels among patients with and without diabetic septic foot; a subanalysis was done to compare vitamin D among hospitalized patients. Random effect was used because significant heterogeneity was observed. Funnel plots were used to assess lateralization. $P < 0.05$ was considered statistically significant.

RESULTS

The current meta-analysis included 12 studies including 7619 patients. The included studies were seven cross-sectional, three prospective, and two retrospective studies; nine were published in Asia and three were from Europe[18-29]. The included studies were of good quality as assessed by the Newcastle Ottawa Scale[30]. Vitamin D was lower among patients with DFUs [odds ratio (OR): -5.77, 95% confidence interval (CI): -7.87 to -3.66; χ^2 was 84.62; mean difference, 9; I^2 for heterogeneity, 89%; $P <$ 0.001, and P for overall effect < 0.001] (Figure 2). Vitamin D level was low when a subanalysis was conducted including only hospitalized patients with diabetes septic foot (OR: -6.32; 95%CI: -11.66 to -0.97; χ^2 was 19.39; mean difference, 2; I^2 for heterogeneity, 90%; $P = 0.02$) (Figure 3). Vitamin D level was lower among patients with DFUs after including studies that controlled for age, sex, duration of diabetes, and HbA1c (OR: -6.32; 95%CI: -923 to -3.42; χ^2 was 18.72; mean difference, 4; I^2 for heterogeneity, 79%; $P < 0.001$) (Figure 4).

DISCUSSION

In the present meta-analysis, vitamin D levels were lower among patients with DFUs compared to their counterparts without FUs (OR: -5.77; 95%CI: -7.87 to -3.66). There were no differences between hospitalized patients and outpatients. The results remained robust when including studies that controlled for age, sex, duration of diabetes, and HbA1c. The quality of the included studies was good[30]. The current findings were in line with a narrative review including three studies[31]. The present findings were similar to the first meta-analysis published by Dai and colleagues in 2019. Dai *et al*[16] found an association between vitamin D levels and DFUs. However, Kota *et al*[32] included studies published by the same authors and some were poster presentations. Yammine *et al*[33] found similar results.

Table 1 Basic characteristics of patients with and without diabetic foot ulcers

Ref.	Study type	Country	Duration	Diabetes	Control	Results
Afarideh *et al*[18], 2016	Cross-sectional, 30, and 30	Iran	-	41.93 ± 45.48	39.94 ± 26.07	Non-significant, 0.487
Çağlar *et al*[19], 2018	Prospective, 58 interventions and 47 controls	Turkey	12 mo	7.9 ± 6.3	11.6 ± 6.5	Lower among diabetes, < 0.001
Dai *et al*[20], 2020	Prospective, 21, and 30	China	9 mo	11.21 ± 5.20	17.73 ± 3.20	Lower among diabetes, < 0.001
Danny Darlington *et al*[21], 2019	Cross-sectional, 67, and 66	India	-	19.38 ± 5.32	21.91 ± 5.16	No significant difference, 0.306
Feldkamp *et al*[22], 2018	Cross-sectional, 104, and 103	Germany	-	11.8 ± 11.3	19 ± 14.4	Lower among diabetes, < 0.001
Gupta *et al*[23], 2016	Retrospective, 50, and 50	India	-	14.25 ± 8.46	21.28 ± 10.98	Lower among diabetes, < 0.001
Tang *et al*[24], 2021	Prospective, 547, and 1174	China	8 yr	35.8 ± 10.98	45.48 ± 12.91	Lower among diabetes, < 0.001
Tiwari *et al*[25], 2014	Cross-sectional, 112 cases, 107 controls	India	-	40.2 ± 3.7	49.4 ± 3.2	Lower among diabetes, 0.06
Todorova *et al*[26], 2020	Cross-sectional, 73, and 169	Bulgaria	-	11.6	13.5	Lower among diabetes, 0.001
Tsitsou *et al*[27], 2021	Cross-sectional, 33, and 35	Greece	-	17.9 ± 6.7	19.8 ± 8.7	Non-significant, 0.329
Wang *et al*[28], 2022	Retrospective, 242, 187	China	34 mo	26.89	35.64	Lower among diabetes, < 0.001
Xiao *et al*[29], 2020	Cross-sectional, 245, and 4039	China	-	36.96 ± 18.03	40.97 ± 17.82	Lower among diabetes, 0.001

Table 2 Age, sex, duration of diabetes, and hemoglobin of patients with and without diabetic foot ulcers

Ref.	Study type	Country	Age	Sex	DM duration	HbA1c
Afarideh *et al*[18], 2016	Cross-sectional, 30, and 30	Iran	Matched	Matched	Matched	Matched
Çağlar *et al*[19], 2018	Prospective, 58 interventions and 47 controls	Turkey	Controls younger	Matched	Controls newly diagnosed	Matched
Dai *et al*[20], 2020	Prospective, 21, and 30	China	Matched	Matched	Matched	Matched
Danny Darlington *et al*[21], 2019	Cross-sectional, 67, and 66	India	Matched	Matched	Matched	Poor glycemic among foot ulcer
Feldkamp *et al*[22], 2018	Cross-sectional, 104, and 103	Germany	Matched	Matched	Matched	Matched
Gupta *et al*[23], 2016	Retrospective, 50, and 50	India	Control was younger	Males high among DM	Lon among diabetes	Poor glycemic among foot ulcer
Tang *et al*[24], 2021	Prospective, 547, and 1174	China	Control was younger	Higher females in control	Lon among diabetes	Matched
Tiwari *et al*[25], 2014	Cross-sectional, 112 cases, 107 controls	India	Matched	Matched	Matched	Matched
Todorova *et al*[26], 2020	Cross-sectional, 73, and 169	Bulgaria	Control was younger	Matched	Matched	NA
Tsitsou *et al*[27], 2021	Cross-sectional, 33, and 35	Greece	Matched	Matched	Matched	Matched
Wang *et al*[28], 2022	Retrospective, 242, 187	China	Control was younger	Males higher among DM	Lon among diabetes	NA
Xiao *et al*[29], 2020	Cross-sectional, 245, and 4039	China	Matched	Females more	Matched	Poor glycemic among foot ulcer

DM: Diabetes mellitus; HbA1c: Hemoglobin A1c; NA: Not available.

Table 3 Newcastle Ottawa scale risk of bias of the included studies

Ref.	Country	Selection bias	Comparability bias	Outcome	Total score
Afarideh *et al*[18], 2016	Iran	4	2	2	8
Çağlar *et al*[19], 2018	Turkey	4	2	2	8
Dai *et al*[20], 2020	China	4	2	2	8
Danny Darlington *et al*[21], 2019		4	1	2	7
Feldkamp *et al*[22], 2018	India	4	2	2	8
Gupta *et al*[23], 2016	Germany	4	2	2	8
Tang *et al*[24], 2021	India	4	2	2	8
Tiwari *et al*[25], 2014	China	4	1	2	7
Todorova *et al*[26], 2020	India	4	2	2	8
Tsitsou *et al*[27], 2021	Bulgaria	4	1	2	7
Wang *et al*[28], 2022	Greece	4	2	2	8
Xiao *et al*[29], 2020	China	4	1	2	7

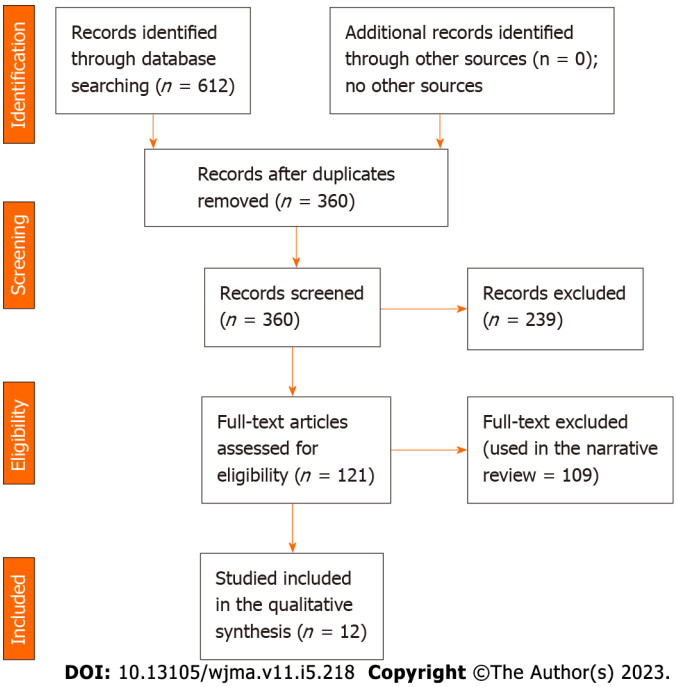

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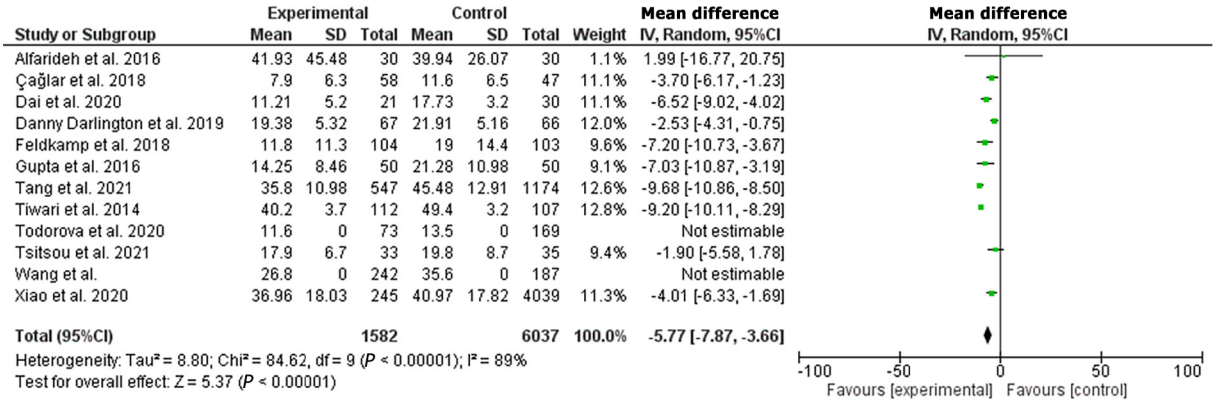
Figure 1 Vitamin D levels among diabetic patients with and without diabetic foot ulcer.

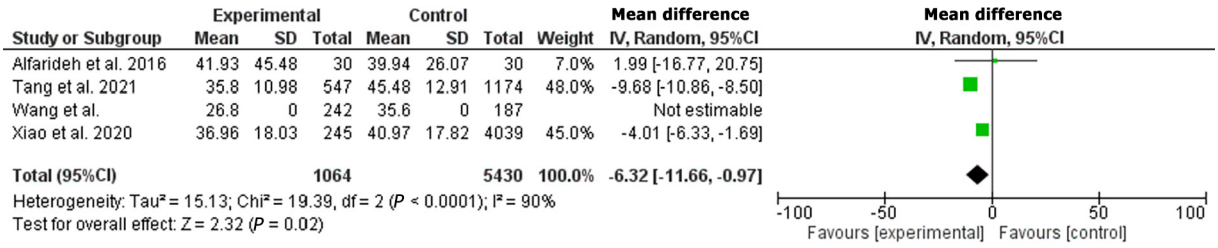
Importantly, Yammine and colleagues included poster presentations, studies published by the same authors, and studies that assessed Charcot's joints[34]. In addition, the previous meta-analysis included Zubair *et al*[35] study in which vitamin D median was reported and not the mean ± standard deviation. A recently published meta-analysis reported similar findings to our results. However, the substantial heterogeneity including posters, research by the same authors, and different primary outcomes limited their results[17]. The main strength of this meta-analysis is the subanalysis on vitamin D among hospitalized patients. Although a single measurement is not enough during stress, the results remain robust even among admitted patients[36].

Vitamin D has been considered a magic bullet and cures many chronic disorders. However, the results were obtained from observational studies. The findings of lower FUs among patients with higher vitamin D may not prove causality. Other confounders might explain the lower vitamin D levels among patients with DFUs including a healthier diet, good exposure to sunlight, and physical activity[37,38]. In addition, vitamin D improves glycemic control among patients with diabetes[39,40]. Thus, high vitamin D may indirectly protect against DFUs by improving glycemic control.



DOI: 10.13105/wjma.v11.i5.218

Figure 2 Vitamin D level among diabetic patients with and without septic foot.



DOI: 10.13105/wjma.v11.i5.218

Figure 3 Vitamin D level among diabetic patients with and without septic foot (hepatized).

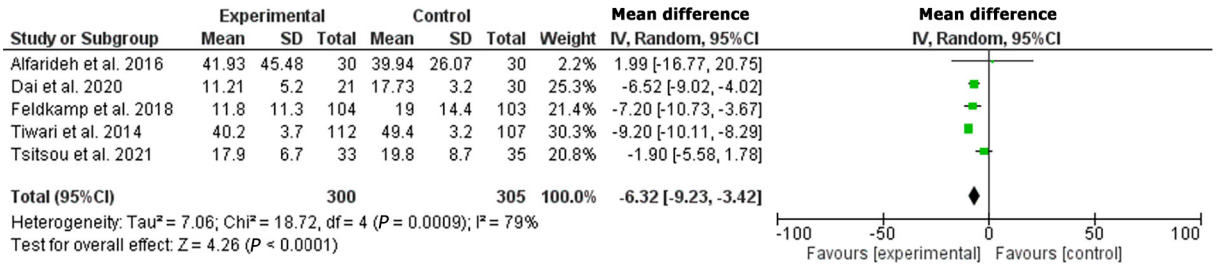


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Figure 4 Vitamin D level among diabetic patients with and without septic foot (controlling for age, sex, duration of diabetes, and hemoglobin).

Osteoblasts (bone formation) and osteoclasts (bone resorption) orchestrate bone remodeling. Osteoclasts genesis activation is through receptor activator of tumor necrosis factor (RANK-osteoprotegerin), ultimately leading to osteolysis and destruction of bone tissue. This pathway is of great therapeutic and clinical implications. Medications that influence different levels of RANK-osteoprotegerin are bisphosphonates, calcitonin, and denosumab. Denosumab is encouraging for the treatment of Charcot diabetic foot. However, bisphosphonates have been evaluated recently due to the adverse events. Calcitonin efficacy is limited[41,42].

In this review, some of the included studies were not matched for age, duration of diabetes, duration of diabetes, or HbA1c. The young age of control subjects, their good glycemic control, and the short duration of diabetes might increase their risk of DFUs.

Vitamin D supplementation and diabetic septic foot

Although, the association between low vitamin D levels and diabetic septic foot was documented. However, the effect of vitamin D therapy on DFUs is unclear. In addition, it is not clear if the relationship is correlated or causal[43]. A double-blinded randomized controlled trial showed that high-dose vitamin D supplementation (170 μg/d) was superior to low doses (20 μg/d) on diabetic ulcer healing[44]. A recent review showed that vitamin D improved diabetic septic foot healing, an effect mediated by the remodeling and proliferation of cells involved. In addition, vitamin D suppresses

proinflammatory responses, enhances antimicrobial peptides, and enhances anti-inflammatory effects [45]. The review by Papaioannou and colleagues, which included 34 studies[46], supported the above findings. A randomized controlled trial published in Asia showed that vitamin D supplementation reduced ulcer length, width, and depth[47]. A recent review of the literature concluded that vitamin D supplementation might slow the progression of neural damage. In addition to the adjuvant role in neuropathic pain and cardiovascular autonomic neuropathy among patients with type 2 diabetes[48].

The current meta-analysis strength is that we included observational studies excluding poster presentations, studies published by the same authors, and studies that used the median of vitamin D. The limitation of this study was the substantial heterogeneity.

CONCLUSION

Vitamin D levels were lower among patients with DFUs compared to their counterparts without ulcers. A low level was observed among hospitalized patients. Randomized control trials investigating the association of vitamin D and DFs and assessing the role of vitamin D supplementation are needed.

ARTICLE HIGHLIGHTS

Research background

Vitamin D deficiency is associated with various disorders ranging from glycemic control to cancer and suicide. Diabetic foot syndrome (DFS) is a common disorder with high morbidity and mortality. The association of DF ulcers (DFUs) with vitamin D deficiency was documented. However, the available meta-analyses were limited by bias and few included studies.

Research motivation

Diabetes mellitus (DM) is approaching an epidemic, the disease is associated with vascular and neuropathic complications. Most people with diabetes are not approaching the recommended targets for cardiovascular risk factors with increasing FUs. DFUs are a preventable disease and vitamin D deficiency is promising. Despite the association of vitamin D deficiency and DM and its complications. However, a cause and effect were not confirmed. In addition, vitamin D supplementation is not without complications and vitamin D is readily synthesized by sun exposure. We included vitamin D supplementation to address this issue.

Research objectives

To assess vitamin D levels among patients with diabetic septic foot and the role of vitamin D supplementation in the treatment of DFS.

Research methods

We searched four databases and included studies other than case reports, perspectives, opinions, and editorials. The studies were included if they assessed the relationship between diabetic foot ulcers and vitamin D levels. The most recent RevMan system was used for data analysis.

Research results

Evidence from observational studies confirmed the association between vitamin D deficiency and diabetic foot ulcers, both among outpatients and hospitalized patients, the associations remained robot after controlling for demographic factors, the duration since the diagnosis of type 2 diabetes, and glycated hemoglobin (odds ratio: -6.32, 95% confidence interval: -923 to -3.42).

Research conclusions

Vitamin D deficiency was associated with DFUs, and vitamin D supplementation was effective in slowing the progress. Various therapies along the RANK-osteoprotegerin pathway are promising.

Research perspectives

The question of vitamin D and the optimal effective dose is elucidated. In addition, future therapies along the RANK-osteoprotegerin might address this dangerous diabetes complication.

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FOOTNOTES

Author contributions: Mirghani HO contributed to the concept and design, literature search, data analysis and interpretation, and manuscript drafting.

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META-ANALYSIS

Evidence relating cigarette, cigar and pipe smoking to lung cancer and chronic obstructive pulmonary disease: Meta-analysis of recent data from three regions

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Abstract

BACKGROUND

There is a need to have up-to-date information for various diseases on the risk related to the use of different smoked products and the use of other nicotine-containing products. Here, we contribute to the information pool by presenting up-to-date quantitative evidence for North America, Europe and Japan and for both lung cancer and chronic obstructive pulmonary disease (COPD) on the relative risk (RR) relating to current *vs* never product use for each of the three smoked tobacco products, cigarettes, cigars and pipes.

AIM

To estimate lung cancer and COPD current smoking RRs for the three products using recent data for the three regions.

METHODS

Publications in English from 2010 to 2020 were considered that, based on epidemiological studies in the three regions, estimated the current smoking RR of lung cancer and/or COPD for one or more of the three products. The studies should involve at least 100 cases of the disease considered, not be restricted to specific lung cancer types or populations with specific medical conditions, and should be of cohort or nested case-control study design or randomized controlled trials. Literature searches were conducted on MEDLINE separately for lung cancer and for COPD, examining titles and abstracts initially, and then full texts. Additional papers were sought from reference lists of selected papers, reviews and meta-analyses. For each study identified, the most recent available data on each product

were entered on current smoking, as well as on characteristics of the study and the RR estimates. Combined RR estimates were derived using random-effects meta-analysis. For cigarette smoking, where far more data were available, heterogeneity was studied by a wide range of factors. For cigar and pipe smoking, a more limited heterogeneity analysis was carried out. Results were compared with those from previous meta-analyses published since 2000.

RESULTS

Current cigarette smoking: For lung cancer, 44 studies (26 North American, 14 European, three Japanese, and one in multiple continents), gave an overall estimate of 12.14 [95% confidence interval (CI) 10.30-14.30]. The estimates were higher (heterogeneity $P < 0.001$) for North American (15.15, CI 12.77-17.96) and European studies (12.30, CI 9.77-15.49) than for Japanese studies (3.61, CI 2.87-4.55), consistent with previous evidence of lower RRs for Asia. RRs were higher ($P < 0.05$) for death (14.85, CI 11.99-18.38) than diagnosis (10.82, CI 8.61-13.60). There was some variation ($P < 0.05$) by study population, with higher RRs for international and regional studies than for national studies and studies of specific populations. RRs were higher in males, as previously reported, the within-study male/female ratio of RRs being 1.52 (CI 1.20-1.92). RRs did not vary significantly ($P \geq 0.05$) by other factors. For COPD, RR estimates were provided by 18 studies (10 North American, seven European, and one Japanese). The overall estimate of 9.19 (CI 6.97-12.13), was based on heterogeneous data ($P < 0.001$), and higher than reported earlier. There was no ($P > 0.1$) variation by sex, region or exclusive use, but limited evidence ($0.05 < P < 0.1$) that RR estimates were greater where cases occurring shortly after baseline were ignored; where bronchiectasis was excluded from the COPD definition; and with greater confounder adjustment. Within-study comparisons showed adjusted RRs exceeded unadjusted RRs. Current cigar smoking: Three studies gave an overall lung cancer RR of 2.73 (CI 2.36-3.15), with no heterogeneity, lower than the 4.67 (CI 3.49-6.25) reported in an earlier review. Only one study gave COPD results, the RR (2.44, CI 0.98-6.05) being imprecise. Current pipe smoking: Four studies gave an overall lung cancer RR of 4.93 (CI 1.97-12.32), close to the 5.20 (CI 3.50-7.73) given earlier. However, the estimates were heterogeneous, with two above 10, and two below 3. Only one study gave COPD results, the RR (1.12, CI 0.29-4.40), being imprecise. For both diseases, the lower RR estimates for cigars and for pipes than for current smoking of cigarettes aligns with earlier published evidence.

CONCLUSION

Current cigarette smoking substantially increases lung cancer and COPD risk, more so in North America and Europe than Japan. Limited evidence confirms lower risks for cigars and pipes than cigarettes.

Key Words: Cigarettes; Cigars; Pipes; Lung cancer; Meta-analysis; Review

Core Tip: For lung cancer, recent North American and European studies indicate current cigarette smoking increases risk > 10-fold in each sex. Limited evidence suggests cigars increase risk about 3-fold, but is variable for pipes. For Japanese studies the risk increase from cigarettes is much less than in Western regions. For chronic obstructive pulmonary disease, cigarettes increase risk about 9-fold, with little sex or regional variation. One North American study reports a lower increase for cigars and pipes. Smoking markedly increases risk of both diseases. While quitting reduces risk most effectively, available evidence suggests switching to nicotine products that are not smoked could potentially reduce these risks.

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INTRODUCTION

It is well-known[1,2] that smoking cigarettes markedly increases the risk of various diseases, particularly lung cancer, chronic obstructive pulmonary disease, ischaemic heart disease and acute

myocardial infarction, and stroke. However, the increase in risk associated with smoking of cigars and pipes, and with the use of other nicotine-containing products is less well characterized. As part of a project comparing relative risks (RRs) of these diseases for current *vs* never use of various products, we have previously published in this journal a review with meta-analysis of the epidemiological evidence relating to the use of snus (Swedish snuff) and of smokeless tobacco[3]. Here we present a systematic review with meta-analysis of the evidence relating both lung cancer and chronic obstructive pulmonary disease (COPD) to current smoking of cigarettes, cigars and pipes based on publications in 2010 to 2020, and a planned further publication will review recent evidence relating current smoking of the same three products to ischaemic heart disease, acute myocardial infarction and stroke. More recently introduced products, such as electronic cigarettes and heat-not-burn products, are not considered in our project at this time, as large long-term epidemiological studies relating their use to the main smoking-related diseases have not so far been conducted. It should be noted that our objective is only to conduct meta-analyses relating to current use of the products considered, and to investigate how the resultant RR estimates vary by other factors, such as sex and region. We do not consider how RRs vary by amount smoked, duration of smoking, or time quit.

The work described in this publication represents a partial update of two earlier meta-analyses we were involved in. One related lung cancer risk to smoking of cigarettes, cigars and pipes, based on publications in the 1900s[4], reporting overall random-effects RR estimates of 8.43 (95%CI 7.63-9.31) for cigarettes, 4.67 (CI 3.49-6.25) for cigars and 5.20 (CI 3.50-7.73) for pipes. The other related COPD risk to cigarette smoking only based on publications up to 2006[5], giving an RR estimate of 3.51 (CI 3.08-3.99). We compare the RR estimates we derive from the more recent publications with these earlier results, and with the findings of various other meta-analyses published in 2000 to 2020[6-18].

MATERIALS AND METHODS

Study inclusion and exclusion criteria

Attention was restricted to publications in English in the years 2010 to 2020 which provided RR estimates for lung cancer or COPD comparing current and never smokers of cigarettes, of cigars, or of pipes. These had to be based on epidemiological cohort or nested case-control studies or randomized controlled trials which were conducted in North America, Europe or Japan, and which involved at least 100 cases of the disease of interest. The studies were excluded if they were restricted to specific types of lung cancer or COPD, or to patients with specific medical conditions, or if the results were superseded by corresponding later results from the same study.

Literature searches

Initially, at stage 0, literature searches were conducted on MEDLINE using simple text searches for publications in 2010 to 2020. For lung cancer the search, carried out on November 7, 2021, used the terms "smoking" and "lung cancer". For COPD the search, carried out on 9th November 2021, linked "smoking" to the term "COPD" or the following terms associated with it – "Pulmonary Disease, Chronic Obstructive", "Lung Disease, Obstructive", "Bronchitis" and "Emphysema".

Then, at stage 1, titles and abstracts were screened to select publications that appeared to describe studies satisfying the inclusion criteria, and both meta-analyses and reviews that may cite other relevant publications. The initial screening was usually carried out by Katharine J Coombs (KJC), with acceptances checked by Peter N Lee (PNL), though in some cases PNL did the initial screening and KJC checked. Disagreements were resolved *via* discussion.

Then, at stage 2, the full texts of the selected publications (and of relevant Supplementary material and other publications linked to them in the MEDLINE search) were obtained, and examined by PNL, who classified the publication as being an acceptance (*i.e.* it appeared to include relevant data), a reject (giving reason), a relevant review or a relevant meta-analysis. The rejections were then checked by KJC, with any disagreements resolved.

At stage 3, additional accepted publications not detected by the MEDLINE searches were sought by examination of reference lists of the accepted papers and of the relevant reviews and meta-analyses and, when obtained, dealt with as in stage 2.

Finally, at stage 4, copies of all the accepted publications (not the meta-analyses) were organized, first by country, and then by study within country, with studies conducted in multiple countries considered as a separate group. The aim was to eliminate from consideration those publications giving results for a study that were superseded by a later publication, and those publications which, on more detailed examination, did not fully satisfy the inclusion criteria.

Data entry

Data were entered into a study database and into an associated RR database. The study-specific information recorded was: Study name; country; region (North America, Europe, Japan or multiple); study design (cohort, nested case-control, or randomized controlled), study population (international, national, regional or specific, *e.g.* workers in a particular industry); study size (number of cases of the

disease); year of start; length of follow-up; sexes considered (males only, females only, or both); and age range considered.

The information recorded relating to each RR was: The RR itself and its 95% confidence interval (CI), the RR and CI being estimated from the data provided if necessary; the study to which it related; an identifier for the paper providing the estimate; the year of publication of the paper; for COPD only the definition of COPD used; the product considered (cigarettes, cigars or pipe); whether the RR related to exclusive use of the product; the sex to which it related (males, females or combined - combined RRs only being entered if sex-specific RRs were not available); the age range considered; the years of follow-up considered; the endpoint (from death certification only, or involving in-life diagnosis); whether a latency rule was applied (*i.e.* whether cases identified in the first few years of follow-up were ignored), and the number of adjustment factors applied to the risk estimate.

Meta-analyses

Meta-analyses could not be conducted relating risk of COPD to current cigar or current pipe smoking as the available data originated from a single study.

Otherwise, individual study RR estimates were combined using fixed- and random-effects meta-analyses[19], with the significance of between-study heterogeneity also estimated.

For current cigar and for current pipe smoking and the risk of lung cancer, where the extent of available data was rather limited, meta-analyses were based on the most adjusted RR estimate per study, with heterogeneity studied by sex and by region.

For current cigarette smoking, where data were much more extensive, more detailed meta-analyses were conducted, as described below.

Initially, meta-analyses were conducted based on either two RR estimates from each study, if separate RRs were available for each sex, or on a single estimate if the study reported only combined sex results or results for only one sex. Where there was a choice of RRs available for a study, those selected were based on a sequence of preferences applied in turn.

For lung cancer the sequence was as follows: (1) Exclusive rather than non-exclusive cigarette smoking; (2) a latency rule had been applied rather than not; (3) the longest follow-up period available; 4) adjustment for the most possible confounders; (5) lung cancer identified by diagnosis rather than death; and (6) separate sex RRs selected rather than the combined sex RR. For COPD the sequence only involved preferences 1, 2 and 6 in turn, due to the more limited data.

For lung cancer the RRs were estimated overall, with heterogeneity studied by the following factors: Sex; region; study population; year of start; study size; exclusive use; latency rule used; study type; lowest age considered; years of follow-up; endpoint; and number of adjustment factors. Grouped levels of the variables were used as appropriate. For COPD, the same factors were studied, except that study type was omitted (all the COPD studies proving to be cohort studies), and that heterogeneity was also studied by definition of COPD (excluding bronchiectasis, including bronchiectasis, or other).

For lung cancer it became clear that RRs were much lower in Japan than in North America or Europe, so these analyses were also repeated excluding RRs from Japan.

While these meta-analyses and heterogeneity investigations were based on variation in RRs between studies, some additional investigations were conducted on within-study variation in RRs, based on data from the same publication. For sex, these meta-analyses were based on the ratio of the RR for males to that for females, while for level of adjustment, results were compared based on the ratio of the RR adjusted for multiple potential confounding variables to the RR adjusted for no variables. Where multiple pairs of results were available within a publication, the pair selected was chosen based on the preferences described above. For within-study variation of other characteristics, where there was far less data available, the results were simply summarized in the text.

RESULTS

Literature searches

Flowcharts of the searches are shown in Figure 1 for lung cancer and in Figure 2 for COPD. Starting with over 10000 papers identified in the initial MEDLINE searches for each disease, 53 study reports were identified for lung cancer and 19 for COPD, which provided results for, respectively, 44 and 18 studies.

For lung cancer there were in total 152 RRs available for analysis, 138 for cigarette smoking, six for cigar smoking and eight for pipe smoking, single studies sometimes providing multiple estimates, *e.g.* for separate sexes, for several levels of adjustment for covariates, or for several products. For COPD there were 58 RRs available for analysis, 52 for cigarette smoking, three for cigar smoking and three for pipe smoking. Table 1 (lung cancer) and Table 2 (COPD) gives some details of the studies considered. Eleven of these studies provided data for both diseases.

Table 1 Details of the 44 studies of lung cancer

Study ID[a]	Ref.	Country	Design[b]	Study Population	Start year	Year followed	Age[c]	Sex[d]	Cases	Adjust[e]	Excl[f]	Latency[g]	Endpoint	NRR[h]
ACE	[51,52]	US	Cohort	Regional	1995	10	18+	C	111	0, 8	0	0	Died	2
AEROBIC	[53]	US	Cohort	Regional	1974	29	20-84	M	232	0	0	0	Died	1
AGRICAN	[54]	France	Cohort	Regional	2005	6	18+	M, F	664	1	0	0	Diagnosed	2
AHS	[55]	US	Cohort	Pesticide workers	1993	18	NAR	C	789	0, 8	x	0	Diagnosed	2
AMIANT	[56]	Poland	Cohort	Asbestos workers	2000	14	NAR	C	110	0	0	0	Diagnosed	1
ARIC	[57]	US	Cohort	Regional	1987	19	45-64	M, F	470	0, 3	0	0	Diagnosed	4
ATP	[22]	Canada	Cohort	Regional	2001	16	35-69	M, F	210	0, 1, 7	0	0, x	Diagnosed	10
BIOBANK	[58]	UK	Cohort	National	2006	10	40-73	M, F	1493	0	0	0	Diagnosed	2
BWHS	[59]	US	Cohort	National	1995	18	21-69	F	306	0, 1, 7	0	0	Diagnosed	3
CHANCES	[21]	Multiple	Cohort	International	1982	29	46-74	C	14041	0, 7	0	0	Diag, died	4
COAL	[60]	US	Cohort	Coal miners	1969	38	NAR	M	568	7	0	0	Died	1
CPS-I	[26]	US	Cohort	National	1959	6	49+	M, F	1293	0, 1, 3	x	0	Died	6
CPS-II	[26]	US	Cohort	National	1982	6	49+	M, F	4957	0, 1, 3	x	0	Died	6
EPIC	[31]	Multiple	Cohort	International	1991	14	35-70	M	2995	0, 5	x	0	Diagnosed	6
	[32]					8	30-70	M, F	2995	7	0	0	Diagnosed	2
ESTHER	[61]	Germany	Nested CC	Regional	2000	17	50-75	C	143	0	0	0	Diagnosed	1
FRAMING	[62]	US	Cohort	Regional	1954	59	NAR	C	284	0, 1	0	0	Diagnosed	2
HBC	[63]	Finland	Cohort	Regional	2001	5	55-65	C	121	1	0	0	Diagnosed	1
HPFS	[64]	US	Nested CC	Medical workers	1986	14	40-75	M	210	0, 2, 4	0	0	Diagnosed	3
JP8	[23]	Japan	Cohort	National	1984	25	35+	M, F	4478	0, 2, 5	x	0, x	Diagnosed	8
JPHC	[65]	Japan	Cohort	National	1990	21	40-69	M, F	1663	0	x	0	Diagnosed	2
	[66]					3	40-69	M, F	1663	0, 10	x	0	Died	4
KAISER	[67]	US	Cohort	Regional	1978	30	NAR	C	1415	0, 6	0	0	Diagnosed	2
KRIS	[68]	Lithuania	Cohort	Regional	1972	36	40-59	M	343	0, 1, 4	0	x	Diagnosed	3
LSS	[69]	Japan	Cohort	Atomic bomb	1950	59	5+	M, F	1597	0	x	0	Diagnosed	2

				survivors									
MWOMEN	[24]	UK	Cohort	National	1996	15	50-69	F	6331	0, 10	x	0, x	Died	3
NHANES	[70]	US	Cohort	National	1988	18	40+	C	269	0	0	0	Died	1
NHIS	[71]	US	Cohort	National	1987	28	18-84	C	7420	0, 11	0	0	Died	2
	[72]					9	25-79	M, F	7420	0, 4	0	x	Died	4
NHS	[73]	US	Cohort	Medical workers	1980	24	34-59	F	1729	1, 13	0	0	Died	2
	[74]					24	38-63	F	1729	0	0	0	Diagnosed	1
NIHAARP	[75]	US	Cohort	Regional	1995	11	50-71	M, F	17846	0, 5	x	x	Diagnosed	4
	[76]					16	50-71	C	17846	0	0	0	Diagnosed	1
NLCS	[29]	Netherlands	Nested CC	National	1986	17	55-69	C	3355	0	0	0	Diagnosed	3
	[30]					20	55-69	M, F	3355	0	0	0	Diagnosed	2
NLMS	[28]	US	Cohort	National	1985	26	35-80	C	3890	0, 1, 5	x	0	Died	8
NLST	[77]	US	Cohort	Construction workers	1998	18	NAR	M	352	0, 2	0	0	Died	2
NONMET	[78]	US	Nested CC	Non-metal miners	1947	50	NAR	M	198	0, 7	0	0	Died	2
NOWAC	[79]	Norway	Cohort	National	1991	24	31-70	F	1507	0, 1, 3	0	0	Diagnosed	3
PLCO	[80]	US	Cohort	Regional	1993	15	55-74	C	1040	0	0	0	Died	1
	[81]					15	55-74	F	1040	6	0	0	Died	1
QRESEAR	[82]	UK	Cohort	National	1998	15	25-84	M, F	32187	0, 6	0	0	Diagnosed	4
SCCS	[83]	US	Nested CC	Regional	2002	14	40-79	M, F	1334	0	0	0	Diagnosed	2
	[84]					7	40-79	C	1334	10	0	0	Diagnosed	1
SHEETME	[85]	Multiple	Cohort	Sheet metal workers	1986	24	NAR	M	808	0	0	0	Died	1
THIN	[86]	UK	Cohort	National	2000	12	30-99	C	1015	0	0	0	Diagnosed	1
THREEC	[20]	Norway	Cohort	Regional	1974	33	20-49	M	858	0, 10	0, x	0	Died	6
	[87]					35	35-49	M, F	858	0	0	x	Died	2
USA5	[26]	US	Cohort	National	1986	24	45+	M, F	11420	0, 1, 3	0	0	Died	6
VETERAN	[88]	US	Cohort	Regional	1987	28	21-89	M	105	0	0	0	Diagnosed	1
VITAL	[89]	US	Cohort	Regional	2000	7	50-76	C	797	0	0	0	Diagnosed	1

VLAGT	[27]	Netherlands	Cohort	Regional	1965	43	20-65	M, F	275	0, 3, 4	0	0	Died	4
WHI	[90]	US	Cohort	National	1993	16	50-79	F	901	0, 1, 15	0	0	Diagnosed	3

[a]Study IDs are ACE: The Adverse Childhood Experiences Study; AEROBIC: Aerobics Center Longitudinal Study; AGRICAN: Agriculture and Cancer Study; AHS: Agricultural Health Study; AMIANT: Amiantus; ARIC: Atherosclerosis Risk in Communities study; ATP: Alberta's Tomorrow Project; BIOBANK: The UK Biobank Study, BWHS: The Black Women's Health Study; CHANCES: Consortium on Health and Ageing: Network of Cohorts in Europe and the United States; COAL: Underground coal miners from 31 US mines; CPS-I: Cancer Prevention Study 1; CPS-II: Cancer Prevention Study 2; EPIC: European Prospective Investigation into Cancer and Nutrition; ESTHER: Epidemiologische Studie zu Chancen der Verhütung, Früherkennung und optimierten Therapie chronischer Erkrankungen in der älteren Bevölkerung; FRAMING: Framingham Heart Study; HBC: Helsinki Birth Cohorts; HPFS: Health Professionals Follow-up Study; JP8: Pooled analysis of eight prospective studies in Japan; JPHC: Japan Public Health Center-based Prospective Study; KAISER: Kaiser Permanente Medical Care Program Study; KRIS: Kaunas–Rotterdam Intervention Study; LSS: Life Span Study; MWOMEN: Million Women Study; NHANES: National Health and Nutrition Examination Survey; NHIS: National Health Interview Survey; NHS: Nurses' Health Study; NIHAARP: National Institutes of Health-American Association of Retired Persons Diet and Health Study; NLCS: Netherlands Cohort Study on Diet and Cancer; NLMS: National Longitudinal Mortality Study; NLST: National Lung Screening Trial; NONMET: Non-metal Mining; NOWAC: Norwegian Women and Cancer study; PLCO: Prostate, Lung, Colorectal, and Ovarian Cancer study; QRESEAR: QResearch database; SCCS: Southern Community Cohort Study; SHEETME: Sheet Metal Workers; THIN: The Health Improvement Network; THREEC: Three counties in Norway; USA5: Pooled analysis of five US cohort studies, VETERAN: Veterans Exercise Testing Study; VITAL: Vitamins and Lifestyle; VLAGT: Vlagtwedde-Vlaardingen Study; WHI: Women's Health Initiative Observational Study; US: United States; UK: United Kingdom.

[b]Nested CC: Nested case-control.

[c]NAR: No age restriction.

[d]C: Results only for sexes combined.

[e]Number of adjustment factors for which RR available (0 = unadjusted, 1 = age adjusted, N > 1 = adjusted for N factors).

[f]x: Results available for exclusive use.

[g]x: Results available with deaths excluded in the early period of follow-up.

[h]Number of RRs available.

Cigarette smoking results

The full details of the results summarized below are given in Supplementary material 1 for lung cancer and Supplementary material 2 for COPD. Below, the results are summarized firstly for lung cancer (see also Table 3) and then for COPD (see also Table 4).

Lung cancer

Data available for cigarette smoking: Each of the 44 studies provided data for current cigarette smoking, with data coming from two publications for nine of these studies. Of the 44 studies, 26 were from North America [24 United States (US), one Canada, and one from both the US and Canada], 14 were from Europe [four United Kingdom (UK), two Netherlands, two Norway, and one each from Finland, France, Germany, Lithuania, Poland, and from multiple countries], three were from Japan, and one from multiple countries in North America and Europe. Thirty-nine were cohort studies, and five were nested case-control studies. Eight studies were of workers in specific industries and one was of atomic bomb survivors, the rest considering regional, national or international populations. As shown in Table 1, the studies varied in regard to various factors, including the start year, the length of follow-up, the ages and sexes considered, the number of lung cancer cases studied, and the extent of adjustment for potential confounding factors.

Meta-analyses for cigarette smoking: In total, data were entered on 138 RRs, with up to 10 per study. The initial meta-analyses for cigarette smoking involved 62 of the RRs, selected based on the preferences described in the methods section. As shown in Table 3 and Figure 3, the overall random-effects RR

Table 2 Details of the 18 studies of chronic obstructive pulmonary disease

Study ID[a]	Ref.	Country	Study Population	Start year	Year followed	Age[b]	Sex[c]	Cases	COPD definition[d]	Adjust[e]	Excl[f]	Latency[g]	Endpoint	NRR[h]
CPRD	[91]	UK	Regional	2003	4	40-89	C	14446	3	0	0	0	Diagnosed	1
CPS-I	[26]	US	National	1959	6	49+	M, F	782	DU	0, 1, 3	0, x	0	Died	6
CPS-II	[26]	US	National	1982	6	49+	M, F	2128	DU	0, 1, 3	0, x	0	Died	6
Finn Twins	[92]	Finland	National	1975	27	17+	C	511	5	0, 2	0	0	Diagnosed	2
JACC	[93]	Japan	National	1988	20	40-79	M, F	285	6	0, 1, 9	0	0	Died	6
KAISER	[94]	US	Regional	1978	28	NAR	C	778	4	0, 6	0	0	Diagnosed	2
MWOMEN	[24]	UK	National	1996	15	50-69	F	1910	2	0, 5	x	0	Died	3
NHS-HPFS	[95]	US	Regional	1976	24	30-75	C	832	1	0	0	0	Diagnosed	1
NIH-AARP	[96]	US	Regional	1995	11	50-70	C	3648	1	0	0	0	Diagnosed	1
NLMS	[28]	US	National	1985	26	35-80	C	2091	2	0, 1, 5	x	0	Died	9
NOWAC[i]	[97]	Norway	National	1991	17	26-71	F	68	2	1, 6	x	0	Died	2
PATH	[98]	US	National	2013	3	18+	C	319	1	0	0	0	Diagnosed	1
SMC	[99]	Sweden	Regional	1997	17	48-83	F	1495	8	0	x	x	Diagnosed	1
THIN	[86]	UK	National	2000	12	30-99	C	3901	9	0	0	0	Diagnosed	1
USA5	[26]	US	Regional	1986	24	50+	M, F	9246	DU	0, 1, 3	0, x	0	Died	6
	[100]				25	50+	M, F	9246	2	0, 5	0, x	0	Died	4
VLAGT	[27]	Netherlands	Regional	1965	43	NAR	M, F	313	7	0, 3	0, x	0	Died	4
WHI	[25]	US	Regional	1993	22	50-79	F	4959	1	0	x	0	Diagnosed	1
WHS	[101]	US	Regional	1993	11	45+	F	1604	1	0	x	0	Diagnosed	1

[a]Study IDs are CPRD: Clinical Practice Research Datalink; CPS-I: Cancer Prevention Study 1; CPS-II: Cancer Prevention Study 2; Finn Twins: Finnish Twin Cohort; JACC: Japanese Collaborative Cohort Study; KAISER: Kaiser Permanente Medical Care Program Study; Million: Million Women Study; NHS-HPFS: Nurses' Health Study and Health Professionals Follow-up Study; NIH-AARP: National Institutes of Health–AARP Diet and Health Study; NLMS: National Longitudinal Mortality Study; NOWAC: Norwegian Women and Cancer Study; PATH: Population Assessment of Tobacco and Health Study; SMC: Swedish Mammography Cohort; THIN: The Health Improvement Network; USA5: Five US Cohort Studies; VLAGT: Vlagtwedde-Vlaardingen Study; WHI: Women's Health Initiative Observational Study and; WHS: Women's Health Study; US: United States; UK: United Kingdom.

[b]NAR: No age restriction.

[c]C: Results only for sexes combined.

[d]Disease definition codes: 1 = Self-report; 2 = ICD-10 J40-44; 3 = GP notes and ICD-10 J41-44; 4 = ICD-9 491, 492, 494-496; 5 = Participants entitled to special reimbursement or regularly used anticholinergics; 6 = ICD-10 J41-J44 J47; 7 = ICD-9 490-2, 494, 496 ICD-10 J40-J44, J47; 8 = ICD-10 J44; 9 = GP notes and ICD codes, unstated; DU = definition unstated; COPD: Chronic obstructive pulmonary disease.

[e]Number of adjustment factors for which RR available (0 = unadjusted, 1 = age adjusted, N>1 = adjusted for N factors).
[f]x: Results available for exclusive use.
[g]x: Results available with deaths excluded in early period of follow-up.
[h]Number of RRs available.
[i]Study included despite only 68 COPD cases as results are available for lung cancer.

estimate was 12.14 (CI 10.30-14.30) based on RR estimates that were highly significantly ($P < 0.001$) heterogeneous.

Table 3 also gives RRs by level of 12 different characteristics of the study or of the RR, with the most striking evidence of variation being for region, where the estimate for Japan (3.61, CI 2.87-4.55) was much lower than those for North America (15.15, CI 12.77-17.96), Europe (12.30, CI 9.77-15.49) or the single study conducted in North America and Europe (13.10, CI 9.91-17.32). This is also shown in Figure 3 (North America, Europe, Japan). There was also much weaker evidence that RRs were higher in studies starting more recently and in those with shorter follow-up periods, where the cigarette smokers may also have smoked cigars and/or pipes, where the endpoint was lung cancer death rather than diagnosis, and where more adjustment factors were taken account of.

When these analyses were restricted to studies in North America and Europe (see detailed results in Supplementary material 1), there was no evidence ($P \geq 0.1$) of variation by sex, region or any of the other factors considered in Table 3 except two. One was whether a latency rule was applied, with a significantly ($P < 0.01$) higher RR (19.52, CI 16.27-23.42) for studies excluding cases occurring shortly after baseline than the RR (13.29, CI 11.42-15.46) for studies considering all cases occurring after baseline. The other was study design, with a significantly ($P < 0.05$) higher RR (14.58, CI 12.71-16.74) based on cohort studies than the RR (10.41, CI 8.04-13.48) based on nested case-control studies.

Within-study comparisons for cigarette smoking: There were 18 otherwise comparable pairs of male and female RRs from the same study (see Supplementary material 1). The male RR exceeded the female RR in 13 pairs, and the random-effects estimate of the male/female ratio was significant (ratio 1.52, CI 1.20-1.92).

There were 36 pairs of unadjusted RR estimates and estimates adjusted for 2 or more covariates. Adjustment increased the RR in 24 of these pairs, and decreased the RR in 12. However, this difference was not significant ($P > 0.1$) and in most cases the effect of adjustment was quite small, with adjustment increasing the RR by a factor > 1.25 in six cases, and decreasing it by the same factor in six cases.

Within the studies considered, current cigarette smoking RRs also varied by four other characteristics: exclusive cigarette smoking; latency; years of follow-up; and endpoint. However, the data available were extremely limited, and some of the variation (and all of it for years of follow-up) related to different publications within the same study, where other characteristics varied as well. When attention was limited to results from the same publication within a study, there was no significant evidence of variation in risk for any of the other three characteristics. Thus, study THREEC[20] reported RRs that were virtually identical for exclusive cigarette smoking (32.58) and non-exclusive cigarette smoking (32.83), while study CHANCES[21] provided RRs for the endpoints died (13.10) and diagnosed (11.50) which clearly did not differ significantly. More data were available for latency, with five pairs of results,

Table 3 Lung cancer and current *vs* never cigarette smoking – results from random effects meta-analyses

Full output table	Factor	Level	No. of RRs	No. of studies	RR (95%CI)	Heterogeneity test by level (NS = $P \geq 0.1$) and trend if relevant
	All		62	44	12.14 (10.30-14.30)	$P < 0.001$
4	Sex	Combined	12	12	12.93 (10.55-15.84)	
		Males	26	26	12.95 (9.82-17.08)	
		Females	24	24	11.32 (8.46-15.15)	NS
5	Region	N. America	34	26	15.15 (12.77-17.96)	
		Europe	21	14	12.30 (9.77-15.49)	
		Japan	6	3	3.61 (2.87-4.55)	
		Multi	1	1	13.10 (9.91-17.32)	$P < 0.001$
6	Study population	International	3	2	14.45 (6.85-30.50)	
		National	25	16	10.26 (8.03-13.12)	
		Regional	24	17	16.27 (13.39-19.77)	
		Specific	10	9	9.71 (5.41-17.42)	$P < 0.05$
7	Year of start of baseline	< 1980	14	10	8.65 (5.83-12.83)	
		1980-89	19	13	12.92 (9.83-16.98)	
		1990-99	16	12	13.45 (9.76-18.53)	
		2000+	13	9	14.38 (11.40-18.15)	NS trend $P < 0.1$
8	Number of cases	< 500	19	16	11.90 (9.55-14.83)	
		500-1999	24	17	11.68 (8.65-15.75)	
		2000+	19	11	12.76 (9.99-16.31)	NS trend NS
9	Exclusive cigarettes	No	45	35	13.47 (11.55-15.72)	
		Yes	17	11	9.50 (6.61-13.64)	$P < 0.1$
10	Latency rule applied	No	51	38	11.93 (9.97-14.28)	
		Yes	11	7	13.13 (8.69-19.83)	NS
11	Study design	Cohort	55	39	12.35 (10.35-14.73)	
		Nested case control	7	5	10.41 (8.04-13.48)	NS
12, 13	Lowest age considered	< 30	15	10	11.30 (7.37-17.33)	
		30-39	11	8	11.41 (7.80-16.70)	
		40-48	14	9	13.29 (9.15-19.30)	
		49+	14	10	13.62 (10.22-18.16)	NS trend without
		Missing	8	8	10.79 (7.64-15.23)	Missing NS
14	Year of follow-up	< 10	11	7	12.63 (8.49-18.80)	
		10- < 15	11	8	16.05 (12.48-20.65)	
		15- < 20	14	11	16.05 (12.69-20.30)	

		20- < 30	15	11	9.08 (6.26-13.15)	
		30+	11	8	9.57 (6.01-15.26)	$P < 0.05$ trend $P < 0.1$
15	Endpoint	Died	23	17	14.85 (11.99-18.38)	
		Diagnosed	39	27	10.82 (8.61-13.60)	$P < 0.05$
16	Number of adjustment factors	None	20	15	9.65 (7.13-13.05)	
		Age only	4	3	11.80 (5.24-26.56)	
		More	38	28	13.68 (11.46-16.34)	NS trend $P < 0.1$

RR: Relative risk; NS: Not significant.

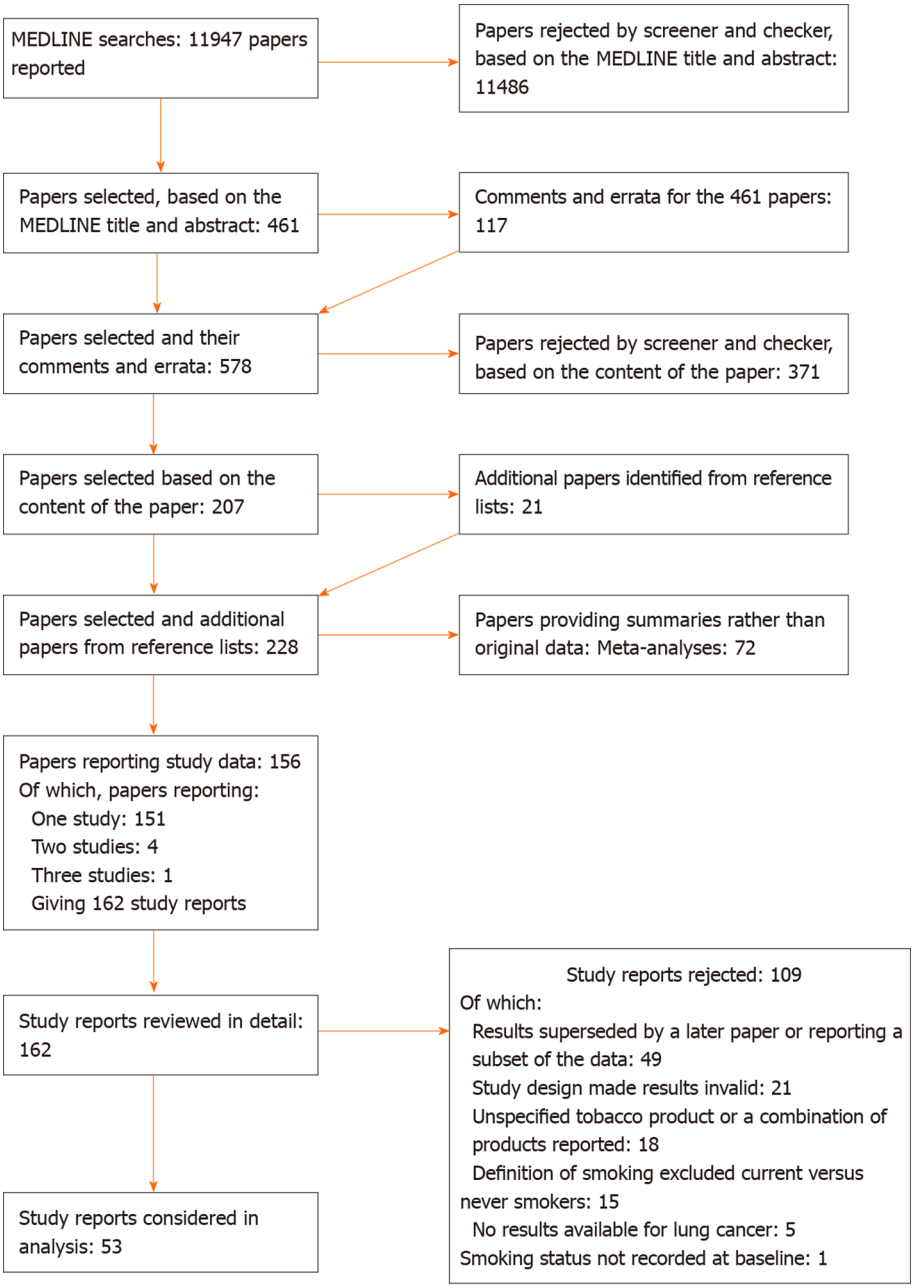

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Figure 1 Literature searches, lung cancer.

Table 4 Chronic obstructive pulmonary disease and current *vs* never cigarette smoking – results from random effects meta-analyses

Full output table	Factor	Level	No. of RRs	No. of Studies	RR (95%CI)	Heterogeneity test by level (NS = $P \geq 0.1$) and trend if relevant
	All		23	18	9.19 (6.97-12.13)	$P < 0.001$
4	Sex	Combined	8	8	8.91 (7.05-11.26)	
		Males	5	5	9.56 (4.22-21.64)	
		Females	10	10	9.33 (4.91-17.71)	NS
5	Region	N. America	13	10	8.91 (5.73-13.84)	
		Europe	8	7	10.63 (6.93-16.29)	
		Japan	2	1	6.00 (2.97-12.12)	NS
6	Study population	National	12	9	8.90 (6.47-12.24)	
		Regional	11	9	9.51 (6.16-14.66)	NS
7	Year of start	< 1988	12	8	10.24 (7.26-14.45)	
	of baseline	1988+	11	10	8.14 (5.78-11.47)	NS
8	Number of cases	< 1000	11	8	7.42 (5.65-9.74)	
		1000+	12	10	10.67 (7.26-15.68)	NS
9	Exclusive cigarettes	No	13	12	9.02 (6.78-12.00)	
		Yes	10	10	9.48 (5.25-17.14)	NS
10	Latency rule applied	No	21	16	8.41 (6.38-11.09)	
		Yes	2	2	21.67 (7.74-60.66)	$P < 0.1$
11, 12	Lowest age considered	< 34	5	5	8.36 (7.13-9.80)	
		35-45	5	4	6.26 (4.31-9.08)	
		46-49	5	3	7.92 (5.41-11.58)	
		50+	5	4	15.36 (5.95-39.66)	NS trend without
		Missing	3	2	9.33 (5.00-17.40)	Missing NS
13	Year of follow-up	< 10	6	4	6.85 (5.24-8.94)	
		10- < 20	6	6	11.32 (6.67-19.20)	
		20- < 30	9	7	10.11 (5.21-19.60)	
		30+	2	1	6.29 (3.73-10.59)	NS trend NS
14	COPD definition[a]	Excl. Bronch	6	5	17.45 (8.35-36.44)	
		Incl. Bronch	5	3	7.83 (4.60-13.35)	
		Other	12	10	7.15 (5.19-9.84)	$P < 0.1$
15	Endpoint	Died	13	8	10.95 (7.42-16.15)	
		Diagnosed	10	10	7.49 (5.63-9.95)	NS
16	Number of adjustment factors	None	8	8	6.96 (5.09-9.53)	
		More	15	10	10.83 (7.67-15.29)	$P < 0.1$

[a]Excl. Bronch: Excluding bronchiectasis (codes 2 and 3 in Table 2); Incl. Bronch: Including bronchiectasis (codes 4, 6 and 7). COPD: Chronic obstructive pulmonary disease; RR: Relative risk; NS: Not significant.

one for each sex from ATP[22] and from JP8[23], and one for females from Million Women Study (MWOMEN)[24]. However (see the estimates in Supplementary material 1) the estimates taking and not taking latency into account were very similar.

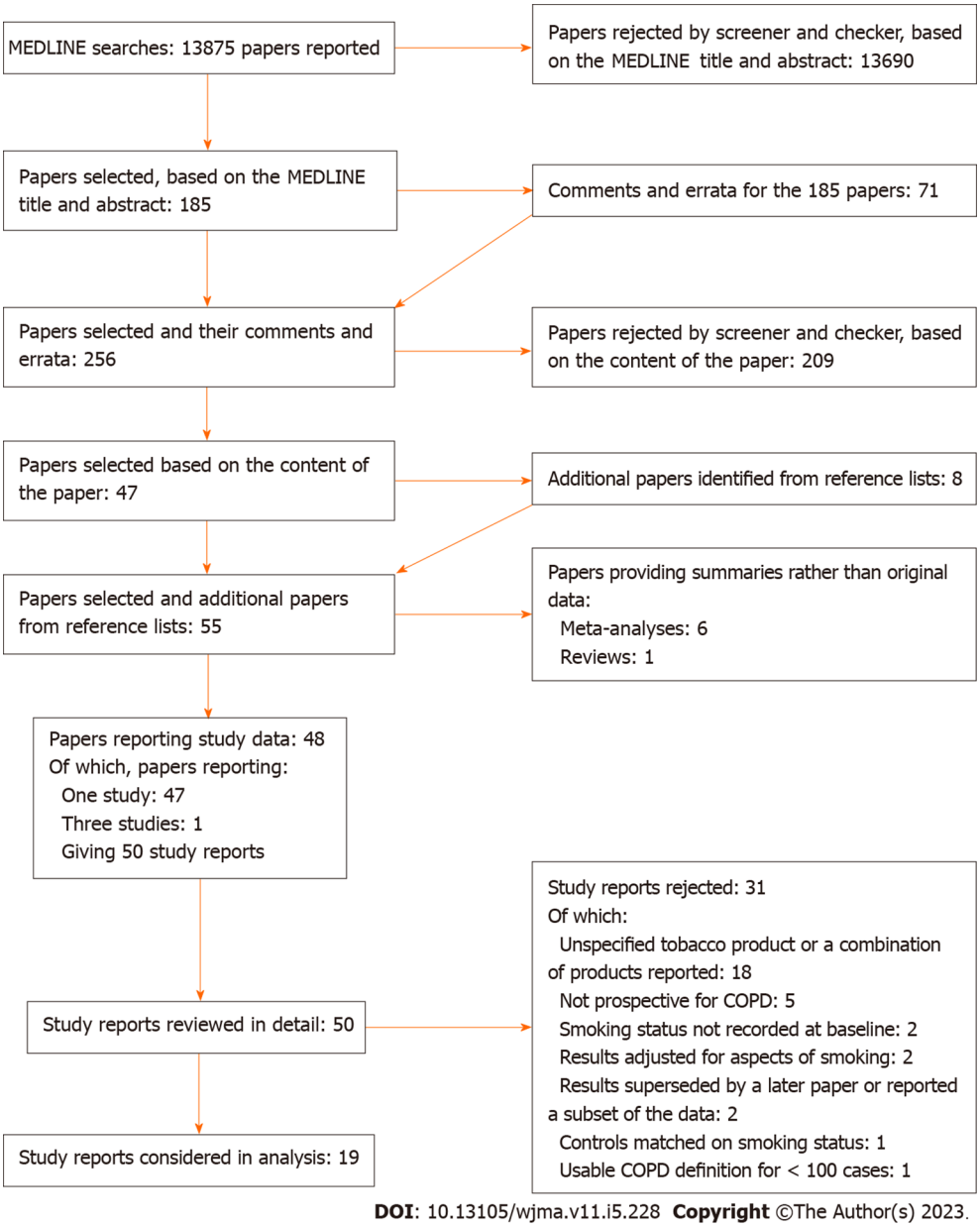

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Figure 2 Literature searches, chronic obstructive pulmonary disease. COPD: Chronic obstructive pulmonary disease.

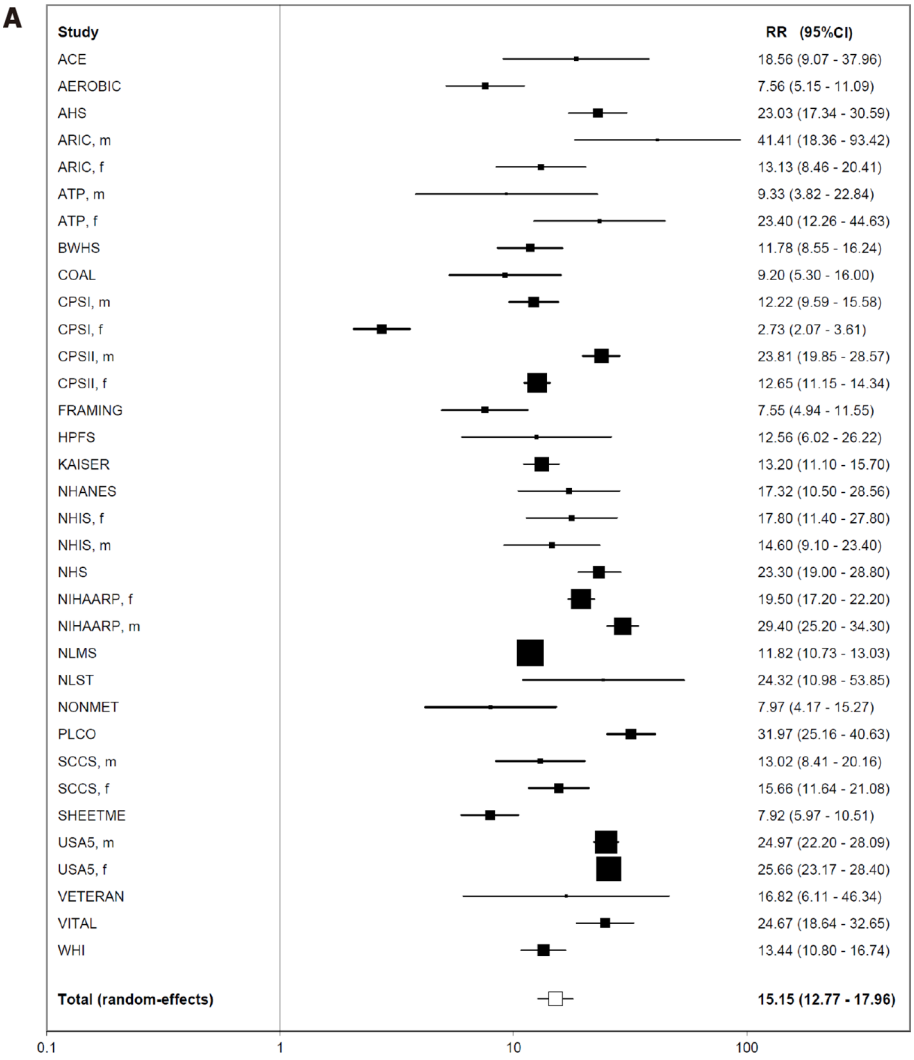
COPD

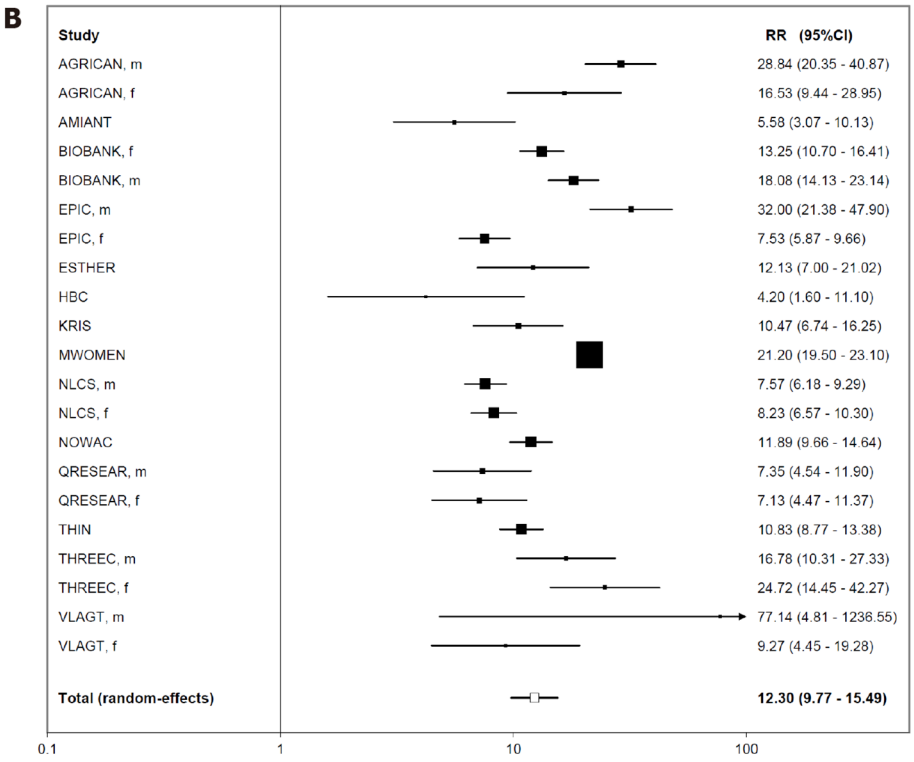
Data available for cigarette smoking: Each of the 18 studies provided data for current cigarette smoking, with data coming from two publications for one of these studies. Of the 18 studies, 10 were from the US, seven from Europe (three UK, and one each from Finland, Netherlands, Norway, and Sweden), and one from Japan. All 18 studies were of cohort design. Nine studies were of national populations and nine of regional populations, with none of workers in specific industries.

As shown in Table 2, the studies varied in regard to several factors, including the start year, the length of follow-up, the ages and sexes considered, the number of COPD cases studied, the definition of COPD used, and the extent of adjustment for potential confounding factors.

Meta-analyses for cigarette smoking: Data were entered on a total of 52 RRs, with up to 10 per study. The initial meta-analyses involved 23 of the RRs, selected based on the preferences described in the methods section. As shown in Table 4 and Figure 4, the overall random-effects RR estimate was 9.19 (CI 6.97-12.13) based on RR estimates that were highly significantly ($P < 0.001$) heterogeneous, the RRs varying from 3.21 (CI 2.96-3.47) in WHI[25] to 36.70 (CI 30.20-44.70) in MWOMEN[24].

Table 4 also gives RRs by level of 12 different characteristics of the study or of the RR. There was some evidence ($0.05 < P < 0.1$) that RRs were greater for three of the characteristics: where a latency rule had been applied; where bronchiectasis had been excluded from the study definition; and where studies had adjusted for potential confounding factors. Nor were they independent, with MWOMEN[24], with its very high RR, having all the three characteristics associated with an increased risk.


A
Study
RR (95%CI)
ACE 18.56 (9.07 - 37.96)
AEROBIC 7.56 (5.15 - 11.09)
AHS 23.03 (17.34 - 30.59)
ARIC, m 41.41 (18.36 - 93.42)
ARIC, f 13.13 (8.46 - 20.41)
ATP, m 9.33 (3.82 - 22.84)
ATP, f 23.40 (12.26 - 44.63)
BWHS 11.78 (8.55 - 16.24)
COAL 9.20 (5.30 - 16.00)
CPSI, m 12.22 (9.59 - 15.58)
CPSI, f 2.73 (2.07 - 3.61)
CPSII, m 23.81 (19.85 - 28.57)
CPSII, f 12.65 (11.15 - 14.34)
FRAMING 7.55 (4.94 - 11.55)
HPFS 12.56 (6.02 - 26.22)
KAISER 13.20 (11.10 - 15.70)
NHANES 17.32 (10.50 - 28.56)
NHIS, f 17.80 (11.40 - 27.80)
NHIS, m 14.60 (9.10 - 23.40)
NHS 23.30 (19.00 - 28.80)
NIHAARP, f 19.50 (17.20 - 22.20)
NIHAARP, m 29.40 (25.20 - 34.30)
NLMS 11.82 (10.73 - 13.03)
NLST 24.32 (10.98 - 53.85)
NONMET 7.97 (4.17 - 15.27)
PLCO 31.97 (25.16 - 40.63)
SCCS, m 13.02 (8.41 - 20.16)
SCCS, f 15.66 (11.64 - 21.08)
SHEETME 7.92 (5.97 - 10.51)
USA5, m 24.97 (22.20 - 28.09)
USA5, f 25.66 (23.17 - 28.40)
VETERAN 16.82 (6.11 - 46.34)
VITAL 24.67 (18.64 - 32.65)
WHI 13.44 (10.80 - 16.74)
Total (random-effects) 15.15 (12.77 - 17.96)
0.1
1
10
100


B
Study
RR (95%CI)
AGRICAN, m 28.84 (20.35 - 40.87)
AGRICAN, f 16.53 (9.44 - 28.95)
AMIANT 5.58 (3.07 - 10.13)
BIOBANK, f 13.25 (10.70 - 16.41)
BIOBANK, m 18.08 (14.13 - 23.14)
EPIC, m 32.00 (21.38 - 47.90)
EPIC, f 7.53 (5.87 - 9.66)
ESTHER 12.13 (7.00 - 21.02)
HBC 4.20 (1.60 - 11.10)
KRIS 10.47 (6.74 - 16.25)
MWOMEN 21.20 (19.50 - 23.10)
NLCS, m 7.57 (6.18 - 9.29)
NLCS, f 8.23 (6.57 - 10.30)
NOWAC 11.89 (9.66 - 14.64)
QRESEAR, m 7.35 (4.54 - 11.90)
QRESEAR, f 7.13 (4.47 - 11.37)
THIN 10.83 (8.77 - 13.38)
THREEC, m 16.78 (10.31 - 27.33)
THREEC, f 24.72 (14.45 - 42.27)
VLAGT, m 77.14 (4.81 - 1236.55)
VLAGT, f 9.27 (4.45 - 19.28)
Total (random-effects) 12.30 (9.77 - 15.49)
0.1
1
10
100

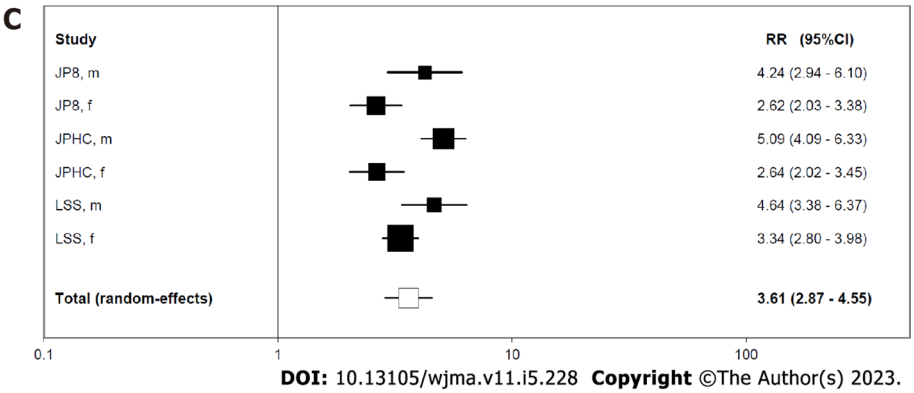


Figure 3 Forest plot for lung cancer and current *vs* never cigarette smoking. A: North America; B: Europe; C: Japan.

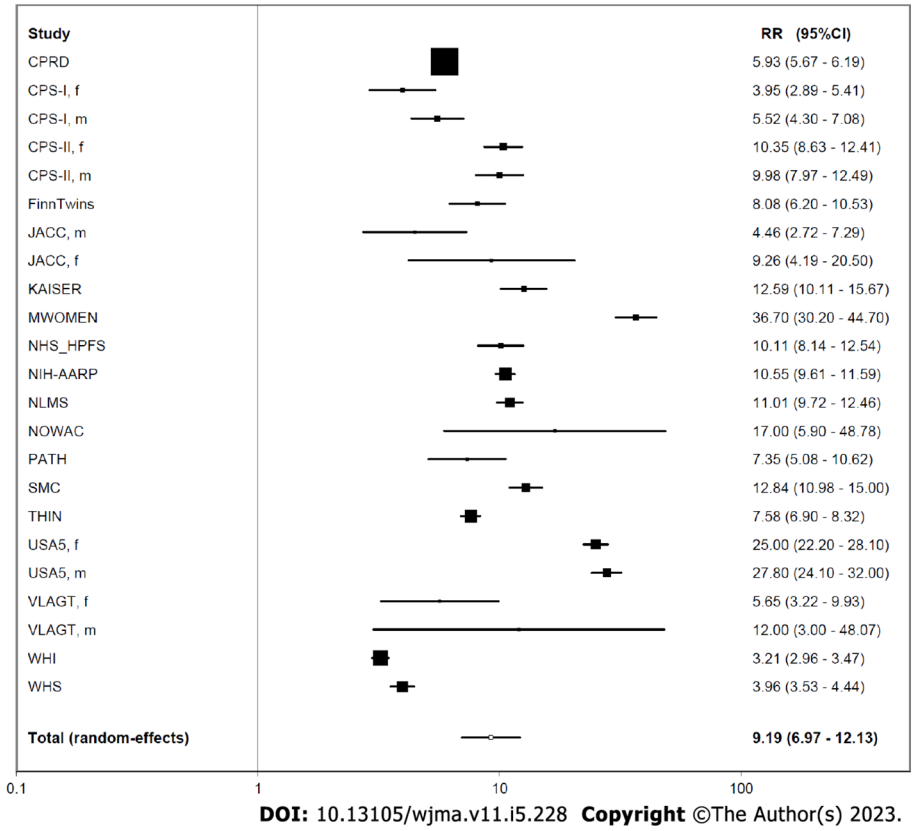


Figure 4 Forest plot for chronic obstructive pulmonary disease and current *vs* never cigarette smoking.

Within-study comparisons for cigarette smoking: There were five otherwise comparable pairs of male and female RRs from the same study (see Supplementary material 2). The male RR was the higher in three pairs, and the female RR was the higher in two, and the random-effects estimate of the male/female ratio was not significant (ratio 1.08, CI 0.88-1.34).

There were 15 pairs of unadjusted RR estimates and estimates adjusted for two or more covariates. Adjustment increased the RR in 13 of these, and decreased it in two ($P < 0.01$), emphasising the conclusion from the previous section. The increase was greater by a factor of 1.5 in 5 of the 14 increases, with a decrease by a similar factor in one case, the adjusted/unadjusted factor varying from 0.65 to 3.17.

Except for in four studies (CPS-I[26], CPS-II[26], USA5[26], VLAGT[27]), where the female RR was taken to be for exclusive cigarette smoking but the male RR was not, the only other characteristic varying within study was latency. Here MWOMEN[24] gave similar adjusted RRs of 35.30 (CI 29.20-42.50) based on analyses involving the whole follow-up, and 36.70 (CI 30.20-44.70) based on analyses excluding occurrences in the first few years of follow-up.

Cigar and pipe smoking results

Lung cancer: The full output for cigar smoking is given in Supplementary material 3. The data are very limited, coming from one study in the US (NLMS[28]), one in the Netherlands (NLCS[29,30]) and one of multiple studies in Europe (EPIC[31,32]), with the RR estimate from NLCS based on far more lung cancer cases in current cigar smokers (520) than seen in NLMS (11) or EPIC (3). Only an unadjusted RR estimate was available from NLCS, while the other studies provided RRs by level of adjustment. All the RR estimates are in the range 2.68 to 4.71, with the combined random-effects estimate, based on the most adjusted data, being 2.73 (CI 2.36-3.15), with no evidence of heterogeneity ($P > 0.1$).

The full output for pipe smoking is given in Supplementary material 4. Again, the data are very limited, coming from the same three studies as for cigar smoking (NLMS, NLCS and EPIC), plus one in Norway (THREEC[20]). The most precise RR estimate comes from NLCS. As for cigars, RR estimates by level of adjustment were available from each study except for NLCS. Based on the most adjusted data the overall random-effect RR estimate was 4.93 (CI 1.97-12.32), the wide confidence interval reflecting the highly significant heterogeneity ($P < 0.001$), with individual study most-adjusted RRs being over 10 for two studies (EPIC 13.30, THREEC 10.32) and under 3 for the other two (NLMS 1.51, NLCS 2.80).

COPD: The data for pipe and cigar smoking, shown in Supplementary material 5, are very limited, coming from only one study, which was conducted in the US (NLMS[28]). This reported combined sex RRs for exclusive cigar smoking *vs* never smoking of 2.21 (CI 0.89-5.47) adjusted for age only, and of 2.44 (CI 0.98-6.05) after additional adjustment for sex, race/ethnicity, education and survey year. The corresponding estimates for exclusive pipe smoking were, respectively, 1.04 (CI 0.27-4.10) and 1.12 (CI 0.29-4.40).

Comparison within study of current cigarette smoking RRs for lung cancer and COPD

There were eleven studies, seven in the US and four in Europe, which provided comparable results for both lung cancer and COPD. For seven of the studies (CPS-II, Kaiser, NIH-AARP, NLMS, THIN, VLAGT and WHI) the RRs were higher for lung cancer than for COPD, while for two (MWOMEN and NOWAC) the RRs were lower. For USA5 the RRs were very similar in both sexes, being slightly higher for lung cancer for females and slightly higher for COPD for males. For CPS-I the RRs were clearly higher for lung cancer in males and slightly higher for COPD in females. (See Supplementary material 1 and 2 for the RRs). These within-study comparisons are consistent with the higher overall RR estimates for lung cancer than for COPD.

DISCUSSION

Lung cancer

Comparison with earlier reviews – cigarettes: Our conclusion that current cigarette smokers have a substantially increased risk of lung cancer is consistent with that of major bodies (*e.g.*[1,2]). Our overall random-effects RR estimate of 12.14 (CI 10.30-14.30) for current *vs* never cigarette smoking is not dissimilar from an estimate of 10.92 (CI 8.28-14.40) from a meta-analysis based on 34 cohort studies published in 2013[13] (though based on current *vs* non rather than current *vs* never cigarette smoking), and somewhat higher than estimates of 7.33 (CI 4.90-10.96) for males and 6.99 (CI 5.09-9.59) for females based on 99 cohort studies published by 2016[16] and of 8.43 (CI 7.63-9.31) based on our earlier meta-analysis, of studies published in the 20th century[4].

We also found much higher RR estimates for North America (15.15) and Europe (12.30) than for Japan (3.61). Strong evidence of regional variation in risk is also evident based on publications in the 20th century[4], where RRs for current *vs* never smoking of any product were 11.68 (CI 10.61-12.85) for North America, 7.53 (CI 5.40-10.50) for the UK, 8.68 (CI 7.14-10.54) for Scandinavia, 8.65 (CI 5.98-12.51) for other regions of Europe, 2.94 (CI 2.23-3.88) for China, 3.55 (CI 3.05-4.14) for Japan and 2.90 (CI 2.04-4.13) for other regions of Asia. Similar, relatively low, RRs have been reported based on meta-analyses conducted in Japan[6,15] or in the whole of Asia[7,17], while relatively high RRs for Europe and the US have been reported in recent meta-analyses or large studies[10,13,33,34]. There is considerable heterogeneity between the estimates from different studies, with, for example, 11 of the 34 selected RR estimates for North America exceeding 20, and 7 less than 10. However, the fact that the highest of our six individual RR estimates for Japan was 5.09 emphasises the regional difference, with a very recent large study in China[35] having also reported similarly relatively low RRs for smoking.

Our analyses show a somewhat higher RR in males than females, with the within-study comparison estimating the ratio as 1.52 (CI 1.20-1.92). A similar difference was also seen in our earlier meta-analyses [4] where the RRs were 9.16 (CI 8.00-10.49) for males and 6.76 (CI 5.65-8.08) for females. Other recent reviews or analyses of large studies have all also reported a higher RR in males, though with one exception, where the RRs from a pooled analysis of case-control studies were 23.6 (CI 20.4-27.2) for males and 7.8 (CI 6.8-9.0) for females[10], the RRs for the others[6,7,15,16] were at most 60% higher in males.

Of the other factors studied in our latest analyses (see Table 2) some were not considered earlier. Of those that were, neither set of analyses showed any clear variation by study size, by study type, by whether the exposed group smoked exclusively cigarettes or not, or by the extent of adjustment for potential confounding factors. There was a tendency for RRs to be greater for studies starting later, more clearly seen in the earlier analyses, a difference which may partially explain why the RRs tend to be somewhat higher for the later than for the earlier analyses.

Comparison with earlier reviews – cigars and pipes: Our combined RR of 2.73 (CI 2.36-3.15) for cigar smoking was based on estimates from only three studies. It is somewhat lower than the RR of 4.67 (CI 3.49-6.25) reported in our earlier review[4] based on 15 estimates, though there the individual study estimates showed marked heterogeneity ($P < 0.001$) with three RRs above 10 and four less than 4, the two having the greatest weight being the RRs of 3.30 (CI 2.68-4.06) and of 5.20 (CI 4.10-6.60) derived from the American Cancer Society CPS I and CPS II studies[36,37]. It is also not dissimilar from estimates of 2.98 (CI 2.08-4.26) from a recent review of US studies[18], of 1.87 (CI 0.53-6.55) from a more recent US study[33,34] and of 2.73 (CI 2.06-3.60) from five US cohorts[14] based on ever *vs* never smoking.

Our combined RR estimate of 4.93 (CI 1.97-12.32) for pipe smoking was based on estimates from only four studies which were markedly heterogeneous ($P < 0.001$). It is similar to that of 5.20 (CI 3.50-7.73) reported earlier[4] based on 12 estimates for current pipe only smoking. These 12 estimates also showed marked heterogeneity ($P < 0.001$), with three RRs above 10 and three less than 4, the two having the greatest weight being that of 5.85 (CI 4.52-7.58) derived from the West European case-control study[38] and of 2.14 (CI 1.46-3.13) from the US veterans study[39]. These estimates are not dissimilar from the more recent estimates of 5.00 (CI 4.16-6.01) from the US CPS II study[40] or of 3.18 (CI 1.35-7.52) from an analysis of five US cohorts[14] based on ever *vs* never smoking.

The available data were too limited to study sources of variation in the results for cigar and pipe smoking in the same way that we addressed them for cigarette smoking.

Comparison of risks by tobacco product: Our results suggested that RRs for current cigar smoking and for current pipe smoking are substantially lower than for current cigarette smoking, though the individual study results for pipe smoking are rather heterogeneous. This conclusion is consistent with the results of our previous review[4]. Although the risks we found for cigar and pipe smoking are lower than for cigarette smoking we agree with McCormack *et al*[31], 2010, who concluded that smoking of these products is "not a safe alternative to cigarette smoking" and suggested that "the lower cancer risk of pipe and cigar smokers as compared to cigarette smokers is explained by lesser degree inhalation and lower smoking intensity". Christensen *et al*[28], 2018, considered that the lower risks for pipe and cigar smoking are probably because "cigar and pipe smokers use these products less frequently per day than cigarette users."

Exceptionally, based on a study in Norway, Tverdal *et al*[20], 2011 concluded that "pipe smoking is not safer than cigarette smoking" but the overall evidence reviewed seems inconsistent with this conclusion. It should be noted that all four of the RRs for pipe smoking given in Supplementary material 3 are lower than the corresponding estimates for cigarette smoking from the same study given in Supplementary material 1 (EPIC 13.30 *vs* 32.00, THREEC 10.32 *vs* 16.78, NLCS 2.80 *vs* 7.57, NLMS 1.51 *vs* 11.82), the results from THREEC being those reported by Tverdal and Bjartveit, 2011[20].

COPD

Comparison with earlier reviews – cigarettes: We found clear evidence that current cigarette smokers, compared to never smokers, have a substantially increased risk of COPD, with an overall RR estimate of 9.19 (CI 6.97-12.13). As for lung cancer, this conclusion of a strong relationship is consistent with that of major bodies (*e.g.*[1,2]). Some earlier reviews have given rather lower RR estimates; 4.01 (CI 3.18-5.05) based on cohort studies published by 2013[13] but for current *vs* non smoking, 3.57 (CI 2.72-4.70) based on studies in Japan published by 2016[15], 3.51 (CI 3.08-3.99) based on studies published by 2006[5] and 3.26 (2.67-3.98) based on studies published by 2014[12].

However, there was considerable heterogeneity between the estimates from the different studies, with the RR estimates varying from 3.21 to 36.70. We found no significant ($P < 0.05$) variation in RR by sex or by region, though the direction of effect – higher RRs in males and in North American and European studies – was the same as that seen more clearly in our earlier review based on 133 studies published up to 2006[5]. Our analyses also found some marginally significant ($0.05 < P < 0.1$) evidence that RRs tended to increase with greater adjustment for potential confounding variables, a finding confirmed by within-study comparisons, but not found in our earlier review[5]. This earlier review also found differing RR estimates of 7.47 (CI 4.63-12.05) for exclusive cigarette smoking, and of 3.06 (CI 2.60-3.60) for cigarette smokers who may also have smoked other products. Though our corresponding estimates of 9.48 (CI 5.25-17.14) and 9.02 (CI 6.78-12.00) are not inconsistent with exclusive cigarette smokers having a higher risk, the difference here was not significant (at $P < 0.05$). As shown in Table 4 there was also marginally significant evidence of increased risk for two factors not considered in our earlier review - where cases occurring shortly after baseline were ignored (so as to avoid an effect of pre-existing symptoms affecting baseline smoking habits), and where bronchiectasis was excluded from the

definition of COPD.

Comparison with earlier reviews – pipes and cigars: We only found one study published in 2010-2020, the NLMS study in the US[28], which reported RRs for current cigar smoking and for current pipe smoking, predominantly occurring in males. The adjusted RRs from this study, 2.44 (CI 0.98-6.05) for current cigar smoking, and 1.12 (CI 0.29-4.40) for current pipe smoking, are imprecise, but seem not inconsistent with earlier published evidence.

For current cigar smoking, a recent review of evidence from the US[18] reported a combined estimate of 1.44 (CI 1.16-1.77) based on four studies, while another review[11], which did not provide meta-analysis results, reported estimates for males from two older studies, 1.30 (CI 0.00-7.45) from the Swedish Census study[41] and 3.70 (CI 1.10-12.0) from the Copenhagen City study[42].

Current pipe smoking estimates from the US included that of 2.36 from the Dorn study[43] (where we derived an approximate CI of 1.12-4.96 from the data provided) and of 2.98 (CI 2.17-4.11) from the CPS II study[40], while estimates from the Swedish study[41] and Copenhagen City study[42] were, respectively, 3.60 (with a derived approximate CI of 2.51-5.14) and 2.40 (CI 0.60-9.60).

Comparison of risks by tobacco product: While the estimates cited above do not allow reliable conclusions as to whether, in the US or Europe, the COPD RR differs between current cigar smokers and current pipe smokers, it is clear that the risks for both products are substantially less than those for current cigarette smokers, where the meta-analysis results shown in Table 4 are 8.91 (CI 5.73-13.84) for the US and 10.63 (CI 6.93-12.24) for Europe.

Comparing risks by tobacco product - similarity of results for lung cancer and COPD

In many ways, the results for the two diseases are quite similar. Thus, our meta-analysis RR estimates for cigarette smoking, 12.14 (CI 10.30-14.30) for lung cancer and 9.19 (CI 6.97-12.13) for COPD, both show a very strong relationship, and indeed every single RR estimate for both diseases shown in the forest plots (Figures 3 and 4) is statistically significantly increased. For both diseases, the meta-analysis estimate for cigarette smoking is also substantially greater than the corresponding estimates for cigar smoking, 2.73 (CI 2.36-3.15) for lung cancer and 2.44 (CI 0.98-6.05) for COPD, and for pipe smoking, 4.93 (CI 1.97-12.32) for lung cancer and 1.12 (CI 0.29-4.40) for COPD, though based on much more limited data. For both diseases, the RR estimates for cigarette smoking are also greater based on studies in North America and Europe than on studies in Japan, most clearly evident for lung cancer. They are also quite similar for males and females, and there is no strong evidence of variation by the other factors studied.

General considerations

While the evidence that cigarette smoking increases the risk of lung cancer and of COPD is absolutely clear, the RR estimates for both diseases show substantial between-study heterogeneity. There are multiple reasons for this, many inter-related, and only some of which we have investigated. Thus, populations in different regions and studies may vary in age and race which may affect precisely what is smoked, the daily amount smoked and the duration of exposure. Males and females may also vary by amount smoked. Study populations may also vary in the extent of exposure to other lung cancer and COPD risk factors, and the extent to which adjustment for this is made in the RR estimation. Variation between studies in the exact definition of the exposed and the unexposed groups is also an issue, only some studies considering exclusive exposure or restricting attention to smoking of some minimum lifetime number of cigarettes. Misclassification of smoking is also an issue, with some of those reporting never having smoked actually being current or former smokers, the studies considered generally not using nicotine biomarkers such as cotinine to check self-reports of smoking. Cohort studies also vary in the extent to which they monitor changes in an individual's smoking over time, some studies only classifying subjects by baseline status, when current smokers may have subsequently quit or switched to other products, including e-cigarettes or heat-not-burn products, and some baseline never smokers may have later taken up smoking. Also, the precise definition of disease may vary between studies, as may changes over time in how lung cancer and COPD are treated, so affecting survival, possibly differently for current and never smokers. Some of these factors may also help to explain variations between our results and those reported in other studies or meta-analyses.

Limitations of our work

While limited to studies in North America, Europe and Japan, our work gives good insight into the magnitude of the RR for current *vs* never use of cigarettes for both lung cancer and COPD, as was the main objective of our meta-analysis. Although heterogeneity of the RR estimates from the individual studies limits the precision of the overall estimates, we have attempted to investigate a range of individual factors that contribute to the heterogeneity. However, it would have been possible to carry out multivariate analyses investigating the extent to which RR estimates varied according to the list of factors studied. For cigar and for pipe smoking, our estimates for both diseases are also limited by the small number of studies that investigated these products. Some limitations are caused by the unfortunate lack of clear definition of the product used in some of the source publications, with the term

"smoking" used variously for any tobacco product use, cigarette smoking or exclusive cigarette smoking. While we have attempted to determine the meaning as best we can, some errors may remain.

Other limitations arose as the objectives of our study were less than those of our earlier meta-analyses of lung cancer studies published in the 20th century[4], or COPD studies published up to 2006[5]. Thus, our investigations did not consider aspects of tobacco smoking, including amount smoked, duration of smoking, age of starting to smoke, the effect of quitting, and risks associated with the use of multiple products. Nor did it consider the role of e-cigarettes which were introduced towards the end of the follow-up period in some of the cohort studies. Nor did it consider results for individual histological types of lung cancer or subgroupings of COPD or for individual types of cigarettes, cigars and pipes. Nor did we attempt to quantify how misclassification of exposure, disease, or confounding variables might have biased the RR estimates.

CONCLUSION

Results from 44 studies published in 2010-2020 confirm the strong association of current cigarette smoking with lung cancer risk, with RR estimates markedly higher for North American and European studies than for studies in Japan, and somewhat higher in males than in females, in cohort than in nested case-control studies, and in studies that excluded cases occurring shortly after baseline. Only limited evidence on lung cancer is available for cigar and pipe smoking, all from North America and Europe. While this indicates lower lung cancer risks than for cigarette smoking, the results for pipe smoking are rather heterogeneous.

Results from 18 studies published over the same period also confirm a strong association of current cigarette smoking with COPD risk, though the RR estimates, which are somewhat lower than for lung cancer, do not vary significantly by region or sex. While the COPD RR estimates are markedly heterogeneous no study or RR characteristic was found that explains a major part of this variation. Only one study, in the US, provided evidence on COPD for current cigar and current pipe smoking, and while this suggested lower risks than for cigarette smoking, its results are uncertain.

It is clear that smoking, particularly of cigarettes, markedly increases the risks of developing lung cancer and COPD. To most effectively reduce these risks, smokers should quit smoking[44,45], though alternative nicotine-containing products may substantially reduce these risks. This is clearest for Swedish snus[46-48] where considerable epidemiological evidence is available. However, it also may be true for much newer products, such as e-cigarettes and heated tobacco products which have toxicant levels that are lower by an average of > 90% compared with cigarette smoke[49]. An earlier expert opinion[50] also considered that e-cigarettes cause about 5% of the harm of cigarettes, and less than the harm caused by cigar or pipe smoking.

ARTICLE HIGHLIGHTS

Research background

While there are extensive data on the risks from smoking, these risks may change over time, and up-to-date evidence is needed for cigarette, cigar and pipe smoking.

Research motivation

To obtain recent evidence comparing the risks of major smoking-related diseases due to the use of various tobacco products.

Research objectives

To summarize data relating current smoking of cigarettes, cigars and pipes in North America, Europe and Japan to the risk of lung cancer and chronic obstructive pulmonary disease (COPD).

Research methods

MEDLINE searches identified English publications in 2010-2020 providing data on risks of one or both diseases relating to current (*vs* never) smoking of cigarettes, cigars or pipes in the three regions. The studies had to be of cohort or nested case-control design or be randomized controlled trials, involve at least 100 cases of the diseases of interest, and not be restricted to specific types of the disease, to patients with specific medical conditions or report results superseded by later results from the same study. Relative risk estimates were extracted for each study and combined using random meta-analyses.

Research results

Results for lung cancer were available from 44 studies and for COPD from 18, predominantly from North America and Europe. For current cigarette smoking, overall RR estimates were 12.14 for lung

cancer and 9.19 for COPD. Estimates were slightly but not significantly higher for males than females. Estimates were relatively low in Japan, particularly for lung cancer, where RRs of 3.61 for Japan compared with those of 15.15 for North America and 12.30 for Europe. No highly significant variations were seen for other factors studied, though for COPD estimates were higher (17.45) where the disease definition excluded bronchiectasis. Few of the studies provided evidence on current cigar or pipe smoking, all from the US or Europe. Estimated RRs for cigar smoking, 2.73 for lung cancer and 2.44 for COPD, and for pipe smoking, 4.93 for lung cancer and 1.12 for COPD, were lower than for cigarette smoking, though based on limited data, with notable heterogeneity for pipe smoking for lung cancer.

Research conclusions

Consistent with evidence from earlier studies, risks for cigar and pipe smoking are much less than for cigarette smoking, both for lung cancer and COPD. Risk of lung cancer from cigarette smoking is much less in Japan than in the US or Europe.

Research perspectives

Smoking significantly increases the risks of developing lung cancer and COPD, with risks highest for cigarette smoking. To most effectively reduce these risks, smokers should quit, though evidence suggests that using alternative nicotine-containing products, such as snus, e-cigarettes and heated tobacco products should also substantially reduce these risks.

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FOOTNOTES

Author contributions: Lee PN planned the study; Literature searches were carried out by Coombs KJ and by Lee PN; Statistical analyses were carried out by Hamling JS and checked by Lee PN; Lee PN drafted the text, which was checked by Coombs KJ and Hamling JS.

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PRISMA 2009 Checklist statement: The authors have read the PRISMA 2009 Checklist, and the manuscript was prepared and revised according to the PRISMA 2009 Checklist.

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