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Educational inequalities in cervical cancer mortality: a systematic review and meta-analysis

Master's thesis in Global Health

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Co-supervisor: Terje Andreas Eikemo

May 2023

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Dedication

To my parents
Andrew and Esther Machado

Acknowledgements

The pursuit of a Master's Degree in Global Health has tested, shaped, and affirmed my passion for health and research. I have been inspired, encouraged, supported, and motivated by so many individuals along the way. This project is for all of us, by all of us.

First, I thank God for His grace which has been immeasurably more than I could ever ask, think, or imagine.

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From the start of this project to its completion, I had in mind cancer survivors, cancer fighters, and those who have lost their loved ones to cancer. This is especially for you.

Abstract

Background: Evidence continues to affirm the educational inequalities in mortality, with individuals that have low educational attainment being most at risk. Education has been found to be a key determinant of adherence to preventive health measures such as cancer screening, due to its influence on people's access to and awareness of such services. While the cancer burden continues to increase across the globe, cervical cancer stands as one of the most preventable forms, yet mortality rates are high with striking disparities between and within countries. There is a need for a comprehensive synthesis on the influence of level of education on cervical cancer mortality. This would serve as an evidence base for policy and intervention efforts seeking to close both the inequality and inequity gap, by identifying those most at risk. This study therefore aims to analyse the relationship between level of education and cervical cancer mortality, including an analysis of the variations across specific regions and sociodemographic characteristics, specifically age.

Methods: This study is a global systematic review and meta-analysis including available literature on the effect of educational attainment on cervical cancer mortality. A comprehensive literature search of 7 databases was completed and pooled studies without any language restrictions. Independent reviewers screened abstracts and full texts for eligibility based on inclusion and exclusion criteria, as well as mapped cervical cancer definitions. Inclusion in this review narrowed down to the presence of individual-level data on educational attainment and cervical cancer mortality, excluding survival analysis. Risk ratios (RR) and mortality rate ratios (MRR) were recalculated for studies reporting effect sizes in odds ratio (OR) for the meta-analysis, along with respective 95% confidence intervals. Educational categories were reclassified as low (ISCED 0-2), medium (ISCED 3-4) and high (ISCED 5-8). Random-effects meta-analyses using high education as the reference group were conducted to evaluate the overall effect of education on mortality, and stratified analyses were conducted to assess this effect by age group and region.

Results: Literature searches resulted in over 47,000 sources screened for inclusion. A total of 30 studies mentioned cervical cancer as a cause of death, and of these, 13 were included in this review. Individual-level data from 11 studies were included in the meta-analyses. Results from the meta-analyses showed an overall risk ratio of 2.41 (95% CI 1.81-3.20) for low education and 1.62 (95% CI 1.18-2.24) for medium education. In the stratified analysis, women with low education in both Northern and Southern Europe had a significant increase in the risk of cervical cancer mortality (RR 1.76, $p < 0.01$ and RR 1.93, $p < 0.01$, respectively). However, only women with medium education in the South had a significant increase in the risk of mortality (RR 1.39, $p < 0.04$) compared to those in the North (RR 1.10, $p=0.68$). The impact of an additional level of education on reducing risk of cervical cancer mortality was greater among women in the North than the South. Regarding age, those aged 25-64 with low education had 5.73 times the risk of mortality ($p < 0.01$), compared to those aged 25 and above, who had 2.11 times the risk ($p < 0.01$).

Conclusion: The results indicate that lower educational attainment is associated with an increase in the risk of cervical cancer mortality, with an additional level of education greatly reducing this risk, particularly in the sub-group analysis by region. There was no significant sub-group difference in risk between the regions considered. Conversely, the sub-group analysis by age suggested a significantly larger risk of cervical cancer mortality for younger cohorts with low education. This study provides the foundation for evidence-based policy that seeks to reduce health inequities and inequalities in both the health and education sector, to promote health and well-being for all.

Keywords: education, cause-specific, cervical cancer, inequality, mortality, health inequalities, inequity, educational attainment.

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Abbreviations

AIDS	Acquired Immune Deficiency Syndrome
CHAIN	Centre for Global Health Inequalities Research
CI	Confidence Interval
EU	European Union
GAVI	The Vaccine Alliance
GBD	Global Burden of Disease
GLOBALCAN	Global Cancer Incidence, Mortality, and Prevalence
HIC	High Income Country
HIV	Human Immunodeficiency Virus
HPV	Human Papillomavirus
HR	Hazard Ratio
ICD	International Classification of Diseases
IHME	Institute for Health Metrics and Evaluation
ISCED	International Standard Classification of Education
JBI	Joanna Briggs Institute
LMIC	Low-and-Middle Income Country
MR	Mortality Rate
MRR	Mortality Rate Ratio
OR	Odds Ratio
PRISMA	Preferred Reporting Items for Systematic Reviews
RR	Risk Ratio, Relative Risk ratio
SDG	Sustainable Development Goal
SE	Standard Error
SES	Socioeconomic Status
WHO	World Health Organisation

1.0 Introduction

1.1 The cervical cancer burden

Cervical cancer has been found to be one of the most preventable forms of cancer. Early diagnosis of the disease, which is caused by persistent infection with high-risk types of human papillomavirus (HPV), allows for effective treatment and management of the condition (1). Vaccines also exist for protection against high-risk HPV types. Despite this, it has emerged as the fourth leading cause of cancer death among women worldwide (1). Globally, an estimated 604 127 new cases of cervical cancer and 341 831 deaths occurred in 2020 (2). Mortality rates of the disease display profound inequalities between regions. Low-and-middle income countries (LMICs) have been disproportionately affected by the disease, as approximately 90 percent of cervical cancer deaths worldwide in 2020 occurred in these regions (3). GLOBOLCAN estimates in 2020 depicted these disparities. The highest mortality rates were observed in eastern Africa (28.6 deaths per 100 000 women-years) and the lowest in western Europe (2.0 deaths per 100 000 women-years) (2). Melanesia as well as South-eastern and South-central Asia also reported relatively high rates of 18.6, 10.0, and 9.6 deaths per 100,000 women-years, respectively. Conversely, other high-income countries (HICs) such as Australia and New Zealand had rates even well below those depicted in Europe, at 1.6 deaths per 100 000 women-years (2).

Despite the lower cervical cancer mortality rates in high income countries (HICs), estimates revealed that inequalities are also evident in these regions. In Europe, significant geographical inequalities were found between countries. Mortality rates were much lower in the Northern, Southern, and Western regions, with rates between 2 and 2.2 deaths per 100,000 women years. The East, on the other hand, depicted almost triple these rates at 6.1 deaths per 100,000 women years (2). It is imperative to note that inequalities in cervical cancer mortality also exist within countries. For example, even with long-established cervical cancer screening programmes and traditions of equitable welfare policies, Nordic countries are witnessing an increase in cervical cancer mortality inequalities, with socioeconomically disadvantaged groups being more susceptible to adverse health outcomes (4). Similarly, high-income countries (HICs) such as the United States have depicted cervical cancer death rates over 2-fold higher among women residing in high-poverty versus low-poverty areas (5).

It is therefore essential to understand the underlying causes of these inequalities and inequities to reduce the global cancer burden equitably and effectively. First, the exposure to risk factors of the disease ought to be considered. To begin with, more than 95 percent of cervical cancer has been found to be due to the human papillomavirus (HPV), the most common viral sexually transmitted infection of the reproductive tract (1). While HPV infection is harmless and clears spontaneously, persistent infection with high-risk HPV can cause cancer of the cervix (6). HPV prevalence varies significantly across the world and the associated factors are geographic, biological, and socioeconomic in nature. A study found that HPV infection rates are almost

two times higher in developing regions than in developed regions (42.2 percent and 22.6 percent respectively) (7). For example, almost half of Central and Southern Asians (57.7 percent and 44.4 percent, respectively) were HPV carriers, and in the Sub-Saharan African region, 42.2 percent, and 32.3 percent of women in Southern and Eastern Africa were HPV carriers, respectively. On the other hand, in almost all European countries, the HPV prevalence was significantly lower, at less than 30 percent, such as in Western Europe, at 3.7 percent (7). It is important to note that the burden of HPV infection has also largely affected socioeconomically disadvantaged groups, resulting in inequalities, even within HICs. In the United States, for example, women who have less income, less education, and are likely to belong to racial/ethnic minorities, namely African Americans, Hispanics, and Asians, bear the highest prevalence of HPV infection (8). These disparities in HPV prevalence between and within regions serve as one explanatory factor for the inequalities in cervical cancer mortality rates.

Evidence further shows that HIV (human immunodeficiency virus) is associated with higher rates of HPV acquisition, decreased clearance of HPV and precancerous lesions, and therefore increased risk of cervical cancer (9). In fact, compared to HIV-negative women, cervical cancer mortality in HIV-positive women is approximately 2 times higher (9). Low-and-middle income countries have disproportionately carried the burden of HIV/AIDS, with more than 80 percent of all people living with HIV (PLHIV) living in LMICs in 2020 (10). Based on this, the inequalities in cervical cancer mortality rates between HICs and LMICs can also be understood. Besides, the HIV burden has been found to disproportionately affect socioeconomically disadvantaged groups. HIV has been found to be concentrated among individuals who have less than a high school education and are unemployed (11). The HIV pandemic has sometimes been coined as a ‘poverty pandemic’, due to prevalence being highest among people who are at or below the poverty level (11). Poverty is strongly linked to education, as the level of educational attainment can determine an individual’s economic prospects. Poverty has been found to constrain individuals’ means to negotiate safe practices, such as condom use, and avoid risky ones, including transactional sex (12).

While HPV infection remains a strong risk factor for the development of cervical cancer, the HPV vaccine is a highly effective primary prevention measure (1). Evidence even suggests that recent studies from the United Kingdom, one of the first countries to introduce the HPV vaccine, show that HPV vaccination reduced precancerous lesions and cervical cancer by almost 90 percent among the first cohorts who received the vaccine (13). The World Health Organization (WHO) launched the Global Strategy to Accelerate the Elimination of Cervical Cancer, the first of its kind in the elimination of cancer (14). The strategy recommends all countries to reach and maintain an incidence rate of cervical cancer below 4 per 100,000 women, and vaccination of 90 percent of girls by the age of 15 years has been outlined as a key strategy towards the achievement of this goal (14). Based on this, HPV vaccination has the potential to reduce the burden of cervical cancer through reasonable uptake, yet there are striking disparities between countries. A meta-analysis revealed that while more than 85 percent of high-income countries have introduced national HPV vaccination programs, less

than 25 percent and 30 percent of low-income and lower-middle-income countries respectively, have done so (15).

HPV vaccine has been described as a unique intervention with substantial challenges (15). A recent study explored health system experiences in implementing the HPV vaccine and observed challenges in health systems and logistical factors, such as insufficient human resources, as well as political factors (16). Sociocultural factors also affected HPV vaccination coverage. Regarding health system and logistical factors, insufficient human resources and capacity of staff have compromised coverage rates. This is sometimes further exacerbated by the incorporation of outreach vaccination strategies where nurses and health workers travel to schools instead of only delivering the vaccine at healthcare facilities (16). On the same note, difficulty reaching 'out of school' girls, also compromises the attainment of high HPV vaccination coverage rates while contributing to inequalities in coverage as girls from financially constrained households are most likely to be out of school (16). As for political will, alongside other competing health priorities, expensive public health interventions such as the HPV vaccine demand more cost-effectiveness and sustainability evidence to convince policymakers. International priorities, pharmaceutical company donations or subsidised vaccination programmes, such as the GAVI Alliance have often influenced political commitment and decision-makers to embark on HPV vaccination programmes (16). This eliminates the health policy decision making process at national level which is grounded in the best available information and reflective of the country-specific burden, to ensure decisions are financially sustainable (16).

As stated earlier, socioeconomic, and cultural barriers are also at play when it comes to HPV vaccination uptake and therefore coverage rates. For example, lower educational attainment which results in low knowledge of HPV and its relation to cancer, has compromised HPV vaccination uptake in low-and-middle income countries (17). These findings are parallel even in HICs where lack of knowledge about the HPV vaccine emerged as a reason for low uptake and completion rates of the vaccine (18,19). Economic status has also emerged as a deciding factor for HPV vaccine uptake due to issues of cost. In Latin America and the Caribbean, the cost of the HPV vaccine has emerged as a significant obstacle for widespread introduction of the vaccine (20). Income emerges as a mediating factor when the association between education and cervical cancer mortality is explored through this dimension. Simply put, educational attainment increases the prospects of employment which increases access to health services such as the vaccine. It is important to note that these barriers are also observed in HICs, in unique or similar patterns, resulting in variations in HPV vaccination rates across different socioeconomic groups. For example, in Denmark, a social gradient regarding education, income and employment status was observed, where decreases in vaccine coverage were associated with girls whose mothers were more disadvantaged (19). Similarly, despite the UK being one of the first countries to implement the HPV vaccine, girls from the most deprived areas were less likely to complete the three vaccine doses. It was further evidenced that women from disadvantaged backgrounds and ethnic minorities miss both cervical screening and HPV vaccination (19). Overall, coverage of HPV vaccination rates is evidenced to be much lower

among socioeconomically disadvantaged individuals, regardless of the country's human development index, due to uptake.

Cervical cancer risk factors also extend beyond viral infection. High parity has been found to be associated with the risk of cervical cancer. Excess risk of cervical cancer among women with high parity is believed to be linked with a high rate of cervical abnormalities during pregnancy and a high detection rate of HPV among pregnant women (21). A systematic review and meta-analysis revealed that women with high parity had higher odds of developing cervical cancer compared to those with relatively low parity (22). Women in poor resourced settings, specifically low-and-middle income countries, relatively tend to have higher parity (23). This is a result of children being needed as a labour force and to provide care for their parents in old age. Further to this, low levels of female education lower their autonomy in making decisions on health behaviours such as using condoms or limit their overall awareness on contraceptive methods (23).

While HPV vaccination stands as an effective preventive measure for cervical cancer, effectiveness of cancer screening programmes also goes hand in hand with this. Screening is the first link in the cancer control chain. The type of cancer screening program (organised or opportunistic) continues to be recognized as an important factor in cancer screening participation (24). According to the WHO, screening programmes are likely to achieve a high coverage of the at-risk population and deliver desired impact at the population level when implemented through an organized approach (25). Organised screening programmes define a target population for screening and systematically invite all eligible members of the population to participate, thus allowing for population-based provision of high-quality services and patient-focused follow-up and referral pathways (25). Many high-income countries (HICs) have adopted the use of organised screening to increase participation rates in cancer screening. For instance, the Council of the European Union continues to recommend screening for cervical cancer as a population-based approach with quality assurance at all levels (26). Nordic countries have been among the pioneers, with programs established in Finland, Iceland, Sweden, Denmark, and Norway since the 1960's, that have significantly reduced the number of cervical cancer cases by 41-49 percent compared to the absence of screening (26).

Despite this potential, the rationale for cancer control programs to prioritize screening to increase the likelihood of early cancer diagnosis assumes the adequate availability of resources and infrastructure, which is not the actual experience in LMICs (27). One essential component of population-based screening programmes is the development of strong infrastructure for screening implementation, specifically; competent health personnel, organisational resources and capacity, and coordinated service delivery (27). Limited health system capacities characterised by being highly fragmented, under-equipped, and under-staffed, alongside competing health priorities in LMICs has often deterred the ability to implement these 'western' models of screening or resulted in their suboptimal performance (28).

Even so, this does not sufficiently explain the extreme disparities in cervical cancer mortality, as LMICs have still necessitated and invested in pragmatic approaches to cancer screening to address the cancer burden. For instance, alternative cost-effective strategies such as visual

inspection with acetic acid (VIA) for HPV detection-based screening, single visit screen and treat, community-based self-administered HPV testing, and mobile treatment provision, have been adopted in the case of cervical cancer (29,30). The lack of cancer screening experts has also been addressed by training community health workers to administer screening tests or procedures and to provide referral to treatment (31). Further, opportunistic cancer screening programmes also exist in some form, for example across South American regions of Cuba, Ecuador, Uruguay, Puerto Rico, and Mexico (27). In some sub-Saharan African regions, opportunistic cervical cancer screening has been provided through existing programmes focused on infectious diseases and maternal and child health, which helps to reach individuals who have decided to seek care (27). National political commitment to addressing the cancer burden in LMICs is also evidenced by the development of national cancer screening guidelines and control strategies, as well as population-based cancer screening programs in pilot phase in countries such as Chile and Argentina (32).

It has been noted that an effective cancer screening programme, regardless of its typology, relies on participation in screening by most of the target population. Cancer screening participation remains low globally (33). This is particularly evident among medically underserved and socially disadvantaged groups, such as rural populations, and racial and ethnic minorities (34). The systemic factors that underlie socially disadvantaged groups, such as no guaranteed right to prevention care as well as financial barriers, have resulted in suboptimal access to healthcare, late cervical cancer diagnosis, and thus low survival rates (35). In HICs, this has resulted in significant social inequalities in mortality rates, despite the relatively lower cervical mortality rates at a global scale. Higher socioeconomic groups have been more capable in taking advantage of early cancer screening, for example, even with long-established cervical cancer screening programmes and traditions of equitable welfare policies, Nordic countries witness increases in cancer inequalities among women (36). Lower educated women have been found to have higher cervical cancer mortality rates compared to their highly educated counterparts who can benefit from effective cancer screening and treatment programmes (36). Holistically, the percentage of women ever screened for cervical cancer in the European region ranges by country from 11 percent to 100 percent, with barriers to optimum screening including out-of-pocket payments, fragmented service delivery (and other barriers of complex health care systems), distance and travel costs, stigma, language, as well as unprofessional treatment by health care workers such as insufficient knowledge and limited cultural competencies (37).

It is important to note that inequalities are still evident at the stage of diagnosis, regardless of the status of screening services (whole or fragmented). In HICs such as Europe, an underestimated driver of disparities in mortality is late-stage diagnosis, as across the region, diagnosis of early-stage cervical cancer ranges from less than 40 percent to over 80 percent (37). A systematic review and meta-analysis further revealed that prevalence of late-stage presentation was 62.60 percent in Africa, 69.30 percent in Asia, 46.51 percent in Europe, and 50.16 percent in North America (38). In that study, education was found to be significantly associated with late-stage diagnosis of cervical cancer. Patients with primary education and above were 61 percent less likely to have the late-stage presentation of cervical cancer than those with no formal education. Even in the case where women are screened and diagnosed on

time, the issue of following up on positive screening results remains (38). Evidence from cytology-based programs has shown that in general, completion of follow-up steps and adherence to recommended time frames is difficult to achieve for women with low socioeconomic level, which constitutes education (39). This has also been the case in HICs, for example, a study in Denmark showed that 58 percent of women being retested attended within the recommended 18 months (40). Low-income groups, recent immigrants, and ethnic minorities are suggested to have the lowest follow-up rates because of the same socioeconomic as well as structural barriers prior to first screening (40). Factors such as low educational attainment and the knowledge gaps as well as economic constraints they expose people to, are still at play after a positive screening result is obtained (41).

Overall, cervical cancer mortality is characterised by a strong socioeconomic gradient both between and within countries. This primarily reflects inequalities in the availability, access, and uptake of effective screening programmes, and thus inequities in mortality rates (42). Education has emerged as a key social determinant in cervical cancer discourse. Studies show that education promotes the adoption of proactive health-seeking behaviours that promote participation in cervical cancer screening, thus increasing the likelihood of early detection (43). The level of education can also determine people's capabilities in accessing healthcare services such as cervical cancer screening as mentioned earlier (43).

Upon considering how the variations in exposure to risk factors results in observed inequalities in cervical cancer mortality, it is important to factor in the aspect of treatment. In addition to cervical cancer being one of the most preventable non communicable diseases, it is also treatable. Treatment includes treatment of precancerous lesions (secondary preventive measure) or treatment of invasive cervical cancer through surgery, radiotherapy, chemotherapy, or palliative care (tertiary prevention measure) (1). The ability to treat precancerous lesions is largely compromised by issues of late diagnosis as well as little to no participation in cervical cancer screening. This leaves tertiary treatment preventive measures as the final pathway for preventing mortality in the case of advanced cervical cancer. It goes to say that cervical cancer mortality rates are not only contingent on the presence and quality of cancer screening programs but also on the availability of and access to cancer treatment.

LMICs have emerged to be resource constrained in tackling the cervical cancer burden. This can be further illuminated by considering radiation therapy, chemotherapy, and surgery. Radiation therapy is normally the first line treatment of cervical cancer (44). However, a systematic review on the capacity of radiotherapy in LMICs revealed that there are inadequate personnel and equipment to meet the demand for radiation therapy in lower-resource settings (45). A survey revealed the average number of teletherapy machines per million people was 0.21 for low-income countries compared with 8.6 for high-income countries (46). Malawi, for example, is said to have the highest mortality related to cervical cancer, with a mortality rate that is double the rate in Eastern Africa and seven times the global rate, but this form of cervical cancer treatment is not available yet (47). Models of care that combine chemotherapy and surgery have therefore been adopted by service providers such as Médecins Sans Frontières (MSF) (44). In the case of late diagnosis, finances and referrals are arranged to neighbouring

countries with radiotherapy. However, this requires significant support and resources, and patients cannot benefit from them on a large scale (44).

As for chemotherapy, much less patients with cervical cancer receive chemotherapy in LMICs compared to HICs. Patient fear of chemotherapy, distance from infusion centres, and poor referral networks, results in patients in LMICs likely to face difficulty with schedules and payments for chemotherapy (48). Educational attainment again prevails as an alleviating or aggravating factor in this case as it can influence individuals' health knowledge and perceptions, as well as secure employment prospects and financial resources for accessing care. Regarding surgery, procedures such as radical hysterectomy are not available in many low-resource settings. In the case where they exist, they are often concentrated in referral hospitals in urban areas, which may result in barriers related to cost, transport, long wait times, poor referral networks, and inability to pay (48). Despite the existence of medical technologies and pharmaceuticals that can necessitate cervical cancer treatment in HICs, the cost of treatment serves as a financial barrier for low-income women and can possibly explain inequalities in cervical cancer mortality within these regions as well. The significance of these financial barriers is evidenced by the existence of health interventions and initiatives focused on understanding and alleviating the burden of out-of-pocket payments as well as underinsurance for health. For example, The National Breast and Cervical Cancer Early Detection Program in the United States seeks to cover 100 percent of treatment and short-term follow-up costs for low-income uninsured and underinsured women (49). Besides, issues of access to treatment services are still predominant and result in evident mortality inequalities. For example, in the European region, 65 percent of the population lacked access to palliative care services due to barriers such as restrictive regulations for access to essential medicines, poor public and professional awareness of how palliative care (including radiotherapy) can help, and cultural and social barriers (37).

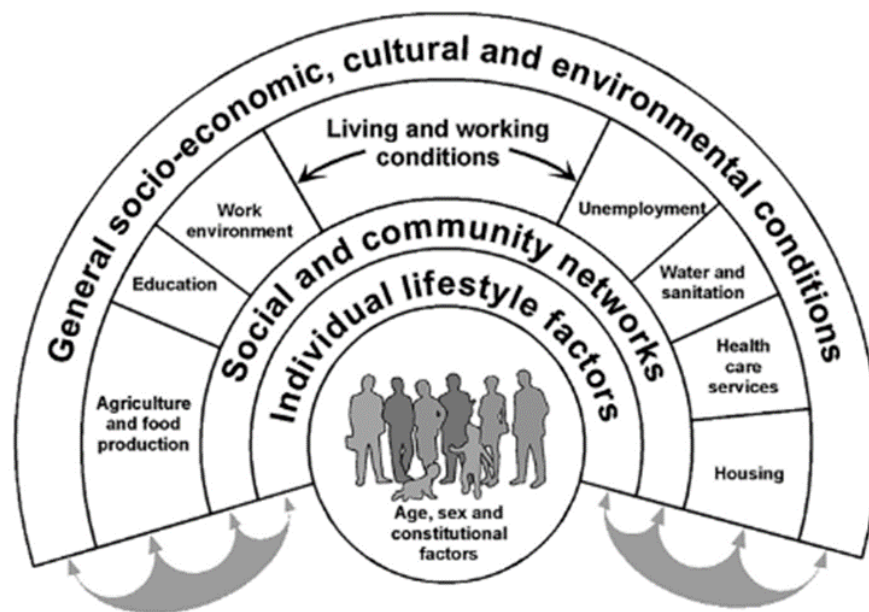
Thus far, it is clear how education is a fundamental determinant of health within cervical cancer discourse. From the exposure to and nature of risk factors to the status of treatment services, issues of health awareness and access to healthcare are linked to one's level of education. Educational attainment, which determines socioeconomic status, entails the vulnerabilities and barriers faced within the healthcare system. It also sets the pathway for the opportunities and challenges faced by individuals in relation to the risk of cervical cancer as well as morbidity itself. Based on this, it is essential to acknowledge the interplay between education and health by considering the theoretical underpinnings of social determinants of health, as well as the inequalities they produce.

1.2 Theoretical foundations of social determinants of health

Six theories highlighting the mechanisms linking education and health will be focused on below. These include the Dahlgren-Whitehead model of health determinants, social causation theory, fundamental cause theory, life course perspective, social selection theory, and the theory of intersectionality.

1. The Dahlgren-Whitehead model of health determinants

The Dahlgren-Whitehead model of 1991 provides a social-ecological theory to health by mapping the relationship between the individual, their environment and disease (49). It acknowledges that health is affected by the interaction between the individual, the community, and overall physical, social, political, and economic environments they find themselves in (49).



Source: adapted from Dahlgren and Whitehead, 1991

Figure 1: Dahlgren-Whitehead model of health determinants

Through illustration, the model highlights the biosocial nature of diseases and determinants of health. This biosocial perspective conceptualizes biological phenomena and social contexts/relationships as mutually constituting forces that should not be viewed independently when understanding aspects of human development, specifically health (50). This perspective has been used to challenge the ‘non-communicability’ of chronic diseases. Scholars acknowledge that while noncommunicable diseases (NCDs) are not infectious or transmissible, their potential to spread epidemically in populations is better understood in terms of their biosocial dynamics embedded in political economy and human biology (51). This interpretation attests that there are limits to the choices open to individuals imposed by their physical, social, and cultural environment, as well as their financial means. These choices can either promote or damage health and well-being (51). As depicted above, the model comprises three levels; the individual level includes individual biology as well as other personal characteristics and lifestyle factors (52). These either increase the likelihood of disease or

promote health and well-being of an individual. The second level comprises a person's closest relationships and networks which influence their behaviour and contribute to his or her experiences, including health and disease (52). Finally, the third level looks at the broad socio-economic and environmental factors, such as education, that favour or impair health and help to create, maintain, or lessen socioeconomic inequalities between groups (52).

2. Social causation theory

Social causation of disease attributes the origin of disease to social conditions and social interactions, thus assuming biological factors are not the sole cause of disease. This notion assumes that social factors such as socioeconomic status, religion, and social networks determine the level and severity of disease and mortality (53). Social causation proposes that unequally spread material, psycho-social and behavioural factors, result in inequalities in health outcomes (53). Education, which is often used as an indicator of socioeconomic status (SES) in health inequalities research, determines the level, scope, and impact of these factors. Material factors are linked to conditions of economic hardship and health damaging conditions in the physical environment, such as housing. Concisely, the more material resources people have, the greater their ability to avoid risk and adopt protective strategies that are available at a given time and a given place (53). For example, the risk of cancer has been found to be lower among those that are highly educated (54). In the case of cervical cancer, a systematic review revealed that cervical cancer screening adherence was more likely among women with high educational levels, thus allowing for early detection and treatment (55). Higher educational attainment means a greater likelihood of being employed with healthier working conditions, better employment-based benefits, and higher wages. Financial hardship has often emerged as a barrier to cervical cancer screening utilisation (55). Be it organised or opportunistic cervical cancer screening services in place, systematic evidence has revealed that minority populations in both low and high-income countries face financial constraints which results in lower screening rates among them (56,57).

Psychosocial factors are the chronic stresses that arise from perceptions and experiences of personal status in an unequal society (53). They also constitute the social, psychological, and interpersonal resources that give people access to coping resources, social support, and cognitive abilities to prevent or handle ill-health consequences. This includes aspects of social standing, social support, as well as sense of control (58). This dimension acknowledges that socioeconomic inequalities in morbidity and mortality cannot be entirely explained by behavioural or material risk factors of disease. Rather, these stressors and resources increase or decrease an individual's vulnerability to disease due to the psychosocial effects they impose on them (53). Sense of control is linked to the perception of personal control, which fosters skills, habits and attitudes that contribute to people's expectations that their own actions shape what happens to them, including health outcomes (58). Social standing constitutes where individuals rank within social hierarchies that reflect status and influence in societies (58). These two factors are directly proportional to the level of education- the higher the educational attainment the greater sense of autonomy and the ability to make decisions on health-related behaviours one has.

Lastly, behavioural factors include health knowledge, literacy, and behaviours (53). They are unevenly distributed between different socioeconomic positions which plays as a determinant of health inequalities. Education level has been found to be directly proportional to the level of health literacy and knowledge, which then determines evidenced health behaviours (59). For example, people have been found to be more likely to engage in health-seeking behaviours such as cervical cancer screening, when they have increased awareness of these services and their related benefits (59). On the same note, health behaviours also tend to cluster in the sense that people who have healthier lifestyles are more likely to engage in preventive health measures such as screening (59). This pre adopted lifestyle can be a result of the influence of education and the health awareness it brings.

3. Fundamental cause theory

Developed in 1995 by Link and Phelan, the Fundamental Cause Theory attempts to describe how social inequality produces health inequality (60). By identifying social conditions as a fundamental cause of disease, the theorists explain the associations between socioeconomic status (SES), morbidity, mortality, and consequently inequalities. To begin with, the theory states that SES functions as a fundamental cause of disease due to two reasons. First, it determines access to important resources that allow individuals to avoid diseases and their consequences, and second, it affects multiple risk factors and disease outcomes that change over time (61). The theory shows that SES has an even stronger association with causes of death that are more preventable, to the extent that resources are critical to the production of social gradients in mortality (61). With cervical cancer, for example, SES factors such as education affect awareness of and access to screening as well as the capacity for taking advantage of treatment services. In contexts with fragile health systems, systemic inefficiencies underlie these socioeconomic realities and increase the likelihood of mortality. Based on these interpretations, population health inequalities have been attributed to social inequality in access to flexible social resources, such as education, that can be used to avoid risks or to minimize the consequences of disease once it occurs (30). Individuals with high social status are said to be able to deploy their resources to avoid disease, seek treatment, and adopt healthy behaviours (60).

The basis of these associations was grounded on assertions by nineteenth-century physicians who founded the field of social medicine. For example, Virchow's declaration that 'medicine is a social science' in 1848 was in part due to the strong association between indicators of poverty and health (60). This was apparent in the dire housing, sanitation, and work conditions of poor people at the time. Medical advances and extensive public health initiatives dramatically reduced the incidence of diseases such as measles, typhoid fever, and tuberculosis (60). Simultaneously, modern welfare states increased people's access to healthcare substantially. As such, by the 1960s, many of the factors that had been identified as linking SES to disease had been addressed. This pointed towards the expectation that the previous association between poverty, social conditions, and health would wane, as evidenced by Charles Kadushin's conclusions in 1964 (60). Kadushin put forth the notion that as countries advance in their standard of living, as public sanitation improves, and as mass immunization proceeds, the gross factors which intervene between social class and exposure to disease would

become more and more equal for all social classes (60). Particularly with reference to the American context, Kadushin declared, individuals from lower classes were no more likely to develop disease than those from the middle or upper classes. However, the SES gradient in health continued to persist due to a parallel shift in risk factors of disease (60). Adler and colleagues in their 1994 review of socioeconomic status and health replaced risk factors of sanitation and immunization that Kadushin mentioned with smoking, exercise, and diet, among others (60). These new behavioural risk factors were evidenced to occur more among specific SES groups after the 1960's. For example, rates of smoking were higher among lower SES individuals. People with higher socioeconomic status were likely to start smoking and more likely to quit due to being better informed about health risks as well as having resources that allowed them to engage in protective efforts to avoid them (60). In the case of cervical cancer, behavioural risk factors such as non-adherence to cervical cancer screening largely occur among lower SES individuals due to limited access to and awareness of health services, as well as low health literacy. Thus, resulting in an educational gradient for cervical cancer mortality.

4. Life course perspective

The life course perspective provides an eco-social approach to disease causation by integrating ecological, social, and biological factors (62). Essentially, this perspective suggests that a multitude of factors across the lifespan determine and manifest disease trends immediately or over the course of time (62). This is a result of social environments having biological influences and being embodied in health. Time serves as an explanatory factor as to how exposures early in life are involved in initiating disease processes prior to clinical manifestations (62). For example, early start of sexual relations, multiple sex partners, as well as early and multiple pregnancies expose women to more HPV strands, including those that are high risk. Yet, the consequences of this continuous exposure are visible only after 15-20 years (63).

Based on this interpretation, the life course model of health recognizes two main mechanisms, namely the critical period model and the accumulation of risk model (64). The critical period model is when an exposure acting during a specific period has lasting or lifelong effects on the structure or function of organs, tissues, and body systems, which are not modified in any dramatic way by later experience (64). While the importance of later life effect modifiers is recognized, it is only in a very simple additive way. Exposures during critical periods earlier in life act as permanent biological programmers to the onset of disease without significant impactful alteration by later exposures or behaviours (64). For example, studies have found that the risk of invasive cervical carcinoma was 2.4-fold among women who reported the age of first sexual intercourse and age of first pregnancy less than 16 years compared with those with an age of first sexual intercourse and age of first pregnancy more than 21 years (65). If women who have early sex and childbearing do not engage in cervical cancer screening due to barriers imposed by low educational attainment, the likelihood of cervical cancer incidence and mortality increase. On the other hand, the accumulation of risk model suggests that factors that raise disease risk or promote good health accumulate gradually over the life course, although there may be developmental periods when their effects have greater impact on health than factors operating at other times (64). While the initiation of sex and childbearing increases the

risk of cervical cancer, high parity which is a progressive factor further exacerbates this risk. Combined with low educational attainment and the socioeconomic disadvantages it entails within the healthcare system, early diagnosis of cervical cancer and access to (quality) treatment services are less likely, thus resulting in mortality. Following this line of thought, it is essential to consider the ways in which exposures at different stages of life, that act independently or interdependently, cluster together in socially patterned ways to produce poor health outcomes.

Scholars have often applied this life course perspective to chronic disease epidemiology. The life-course approach to understanding cancer screening recognises the complex interplay of early life factors, including parental and individual SES in shaping health behaviour (64). This is either directly through financial resources and healthcare access or indirectly through awareness of cancer screening recommendations which is necessitated by education (64). The WHO's Study on Global Ageing and Adult Health (SAGE) examined socioeconomic status (SES) over the life-course in relation to cancer screening in lower-income and middle-income countries (66). Individual and parental SES were assessed based on education and employment measures. The change in SES (social mobility), from parent to individual was assessed based on education and employment measures. It was found that higher individual, parental and life-course SES was positively associated with cervical cancer screening. Further, education-based SES measures emerged to be stronger predictors of screening compared with employment-based measures (66).

5. Social selection theory

The social selection theory implies that health determines socioeconomic position, rather than the reverse. Thus, healthier persons move towards better socioeconomic positions, compared to those that are less healthy, leading to inequalities (62). This theory recognizes a pattern of social mobility, where an individual's social position can change within a lifetime. This change can be compared either with his or her parents' social status (intergenerational mobility) or with himself/herself at an earlier point in time (intra-generational mobility) (53). Chronic illness and disability have been found to have negative socioeconomic effects on individuals and their households which is largely attributed to the economic costs attached to managing the disease (67). The severity of economic hardship is largely dependent on the status of health, social and welfare policies. For example, receiving government disability and sickness related payments can alleviate the economic stressors imposed by chronic illness (34). Simultaneously, chronic illness, and the disability associated with it, can also affect people's ability to fully participate in the workforce (68). These factors have negative implications on an individuals' socioeconomic position.

Education is often used as a proxy measure of socioeconomic status (SES) in health inequalities research. Thus, evident SES inequalities in cervical cancer mortality research can possibly be explained through this theory. It is important to note that the notion of health determining socioeconomic position has been challenged. This is grounded on the basis that people who move downwards because of their health still have better health and social standing than those in the class of destination (53). Similarly, people who move upwards still have a lower social

standing and health than those in the class of destination. Based on this argument, there is no consensus on the influence of social selection and mobility on inequalities in health. Some scholars argue that this phenomenon does not widen health inequalities but rather acts to reduce their magnitude, whereas others do not (53). Some studies conclude that health selection cannot be regarded as the predominant explanation for health inequalities all together (53).

6. Theory of intersectionality

The theory of intersectionality provides an approach to understanding how relationships between societal and individual factors shape health and wellbeing (69). Through this lens, discourse on health inequalities emphasises how individuals' multiple identities such as gender, age, and socio-economic status interact with social systems of power in diverse and changing contexts (69). By acting interconnectedly, these identities create experiences of oppression or privilege. Oppression or privilege from the healthcare angle is grounded on the ability to access and take advantage of available healthcare services without any constraints (69). For example, a systematic review on intersectionality in cancer care found that patients with intersectional identities often experience barriers to cancer care that adversely impact screening, diagnosis, treatment, as well as survivorship (70). Scholars have often used this theoretical foundation to understand cervical cancer screening utilisation among underserved and socially disadvantaged groups (71,72). This is based on the acknowledgement of the intersections of factors such as health literacy levels, socioeconomic status, and demographic characteristics which act as risk factors for poor health outcomes. Inequalities in cervical cancer morbidity and mortality can be explained through the intersectional identities of gender, education level, and age among others.

Regarding gender and education level, there are factors that alleviate or mitigate the structural (dis)advantages women encounter with the disease. While cervical cancer is an illness that can only affect women biologically, gender constitutes the social realities and characteristics women experience due to their sexual identification. The disadvantages range from the lack of autonomy to make healthcare seeking decisions because of gender relations, to low health awareness needed to take advantage of available health care services due to low educational attainment (73,74). For example, among the barriers to cervical cancer screening among women in LMICs, men's disapproval of cervical cancer screening, with some refusing for their wives to be screened, has emerged as a cultural barrier (73). These findings were parallel among urban racial and ethnic minorities in HICs as well (75). This is linked to the aspects of sense of control and social standing alluded to in the social causation theory, which are determined by one's level of educational attainment.

Age has emerged as a prominent factor in cervical cancer screening utilisation discourse. The WHO proposes a global elimination threshold of four cases per 100 000 women-years through the implementation of a triple intervention strategy that is disaggregated by age (76). It consists of vaccinating at least 90 percent of girls against HPV by the age of 15 years, screening 70 percent of women using a high-performance test by 35 years of age and again by 45 years of age (76). A review and synthetic analysis assessed the coverage of different screening programmes according to age groups, as well as the proportions of age groups that have never

been screened before (76). While some studies have found an association between age and cancer screening utilisation, other studies have not (77,78). This has been a result of the interplay of other factors such as marital status, number of life-time sexual partners, knowledge about screening, and socio-economic status among others. This affirms the notion that age also works as an intersectional individual factor across contexts and can illuminate variations in screening utilisation for more targeted approaches.

1.3 Gender, education, and the cervical cancer burden

The theory of intersectionality provides the rationale of how relationships between societal and individual factors shape health and wellbeing through intersectional influence. In theories previously explained, education has emerged as a socioeconomic resource that determines people's ability to access healthcare services, through the provision of knowledge and financial capacities based on employment. Gender emerges as a confounding factor in the relationship between education and employment. It influences both educational attainment and the level of employment secured by an individual or their lack of engagement in paid work. Gender gaps in education and income have been a result of historical societal norms and stereotypical beliefs that have favoured men (79). Significant progress has been made towards bridging the inequity gap in education through gender mainstreaming initiatives in health and social policy as well as welfare state reforms. For example, the widespread availability of contraceptive methods has enabled women to delay childbirth, the spread of anti-discrimination laws and regulations has addressed gender discrimination in education and the labour market, and the increased demand for female labour due to the service sector's growth has changed women's qualifications (79). In many Western countries, there have been growing advantages for women's education, to the extent of women's education surpassing that of men in countries such as the United States of America and some parts of Europe (80). While much progress has been made, large gender gaps still exist in education in many settings, most often at the expense of girls. Women still account for almost two-thirds of all adults unable to read (81). Yet again, despite progress being made towards bridging the gender gap in education, the glass ceiling women encounter in the labour market has not been diminished (79). For example, in the United States, 57 percent of higher education students are women, but women's unadjusted median earnings are 78 percent of men's (79). Similarly, in 26 out of former 28 EU countries, there are more women than men in higher education institutions, but women's unadjusted average earnings are lower than men's in all 28 countries (79).

1.4 Education and cervical cancer screening utilization

The question of whether education is associated with good health continues to influence a growing body of research (80). The education-health gradient for individuals continues to grow over time. This is largely attributed to the health inequalities produced by educational attainment across morbidity and mortality patterns of diseases (80). People who are well educated have been found to experience better health as reflected in high levels of self-reported health and low levels of morbidity, mortality, and disability. Contrarily, low educational attainment is associated with self-reported poor health, shorter life expectancy, and lower survival rates when sick (80). The prominence of education as a social determinant of health

in cervical cancer discourse can be evidenced by the existence of educational interventions used to promote utilisation of screening services (82). This strategy aims to increase people's knowledge about screening services, thus promoting health-seeking behaviour that enables early detection and treatment. The presence of such interventions, or the lack thereof, still does not suffice in understanding and addressing inequalities in cervical cancer mortality. The influence education has on health outcomes is complex and intersectional. With reference to several of the theories highlighted above, education is both a material resource and marker of socioeconomic standing that determines people's capacity to take advantage of healthcare services. Simply put, availability and awareness of health services such as cervical cancer screening does not entail optimum utilisation due to other disadvantages imposed by the level of education one has.

The relationship between education and health can be summed up according to three mediators: economic; social, psychological, and interpersonal; and finally behavioural health (80). Through these mechanisms, the likelihood of cervical cancer screening utilisation can be determined. Further, they reveal the pathways through which inequities in cervical cancer mortality, because of late presentation and diagnosis, occur. Addressing disparities in cervical cancer mortality requires targeted efforts to equitably improve cancer care delivery across the care continuum; from detection, through treatment, and to survivorship (34). This entails measures of relative mortality rates of different population groups, ranged by their education.

1.5 Rationale of the study

There is a consensus on the role of education as a social determinant of cervical cancer mortality. However, there is a need to systematically gather and synthesise all available studies on this to uncover and clarify the influence of level of educational attainment on cervical cancer mortality globally because available evidence only focuses on country or continental level. By understanding the degree to which cervical cancer mortality varies across each level of education, efforts towards global cancer control and the reduction of health inequalities will be more targeted. This would enable fulfilling the Sustainable Development Goals (SDGs). Particularly SDG 3 which aims to ensure healthy lives and promote well-being for all ages, and SDG 10, which seeks to reduce inequalities within and among countries (83). Further, it also facilitates the promotion of SDG 4 and 5, which are targeted towards the promotion of education and gender equality, respectively (83). Ultimately, this research would serve as a strong evidence-base for health policy decisions and prioritisations.

1.5.1 Hypothesis

We hypothesise that there is a statistically significant effect of one additional year of educational attainment on cervical cancer mortality, with inequalities being the highest between top and bottom levels of education. We also hypothesise that this effect varies with age and region.

1.5.2 Aim

The aim of this study is to analyse the relationship between the level of educational attainment and cervical cancer mortality at the global level.

1.5.3 Specific Objectives

1. To systematically search existing literature exploring the association between educational attainment and cervical cancer mortality at the global level
2. To conduct a meta-analysis of included articles
3. To examine variations of this association by age and region

1.5.4 Research Questions

1. Is lower educational attainment associated with increased cervical cancer mortality?
2. If so, how does this association vary with age and region?

2.0 Methods

A systematic review and meta-analysis were carried out to answer our research questions. Through the systematic review, literature was identified, summarised, and critically reviewed. The meta-analysis then yielded an overall statistic which was a combination of all effect sizes reported in studies included in the analysis. This analysis facilitates improvement in precision of effect measures by mapping the association between level of educational attainment and cervical cancer mortality and could answer questions not posed by individual studies (84). Besides, the systematic review can also guide or inform policy change within the education sector to reduce cervical cancer mortality, due to the explicit methodology for search strategy, as well as inclusion and exclusion criteria which provides a robust summary of evidence (85).

2.1 Search strategy

A systematic search of the literature was carried out in Pub-Med, Web of Science, Scopus, EMBASE and Global Health (CAB), EconLit and Sociology Source Ultimate databases in May 2021. The search was limited to papers published since 1980 without any language limitation. Pilot searches were conducted previously to first identify 40 key papers on educational inequalities in adult cause-specific mortality. The search was constructed using key terms: education, socioeconomic status, health inequalities, adult, mortality, and death. The specific search string contained commonly related terms and synonyms to the key terms above. Rather than using the Boolean term “AND” for the search string, a proximity search set to 10 was used instead. This ensured the two words or blocks must occur within ten words of each other, to yield a more relevant and manageable result. An example of the search strategy used in Web of Science is presented in **appendix 1**.

2.1.1 Snowball hand searching

The systematic literature search also captured other systematic reviews and narrative reviews. Although these study designs were not included in the final extraction and analytical phases of

this review, they were not outright excluded in the initial phases leading up to abstract and full-text reading. If a review included at least one article that looked at a social axis and cause-specific mortality, it was screened, in pairs, to search for relevant articles and references that may have not been captured by the original systematic search. Abstracts of these identified ‘snowball’ articles were then read and decided on in pairs. The unique articles identified and included then went on to full-text screening in pairs, and those included went on to the final set of included articles for extraction.

2.2 Inclusion and exclusion criteria

The eligibility criteria for inclusion in the review to examine the relationship between level of educational attainment and cervical cancer mortality is explained below. The criteria were developed and organised according to the SPIDER framework, which consists of the Sample, Phenomenon of interest, Design, Evaluation, and Research type.

Sample: Only participants aged 18 and older were included in the study. If there was uncertainty surrounding the ages of the participants, descriptive characteristics and mean age of participants (if reported) were consulted to determine the likelihood of inclusion of participants below 18 in the specific study. There was no limitation on the sample size and characteristics of the included studies.

Phenomenon of Interest: Studies measuring educational attainment and cervical cancer mortality were included in this review. As this study was conducted in partnership with the CHAIN global systematic review on educational inequalities and cause-specific adult mortality, studies on the cause of interest for this review, namely cervical cancer, were identified upon inclusion in the full article screening to proceed with extractions for the analysis. It is important to note that while some studies included cervical cancer as a cause for adult mortality, the effect measure(s) of interest was an aggregate of other types of cancers or diseases as well. These ‘all-cancer’ or ‘all-cause’ mortality outcomes were excluded because a sole extraction mapping the educational inequalities in cervical cancer mortality was not possible. Besides, education level could be measured through years of education or by categorical educational level such as primary school, secondary school, and so on. Studies that aggregated educational attainment with other socioeconomic indicators were excluded because the effect of education could not be isolated.

Design: This systematic review included most study designs with the exclusion of case-crossover and ecological studies, as outlined in the following abstract and full article screening sub-section below. Ecological studies collect data at the population or group level rather than at the individual level (86). Since this study aimed to examine the relationship between one’s educational attainment and cervical cancer mortality, individual-level data was set as a key criterion for inclusion. Case-crossover studies, on the other hand, are used to determine the effect of an exposure on the onset of an outcome while the individuals themselves act as their own control (86). The basis of

this study design is to investigate exposures that are intermittent instead of constant and have a transient effect. As such, since educational attainment, our exposure variable, is constant and unvarying, a case-crossover design would not apply to our research aim. Included study designs were randomised controlled trials (RCT's), non-randomised controlled trials (pre-post with or without comparison), prospective cohort, retrospective cohort, case-control, case-cohort, and cross-sectional.

Evaluation - Outcomes of interest for measuring educational inequalities in cervical cancer mortality in this study were only individual level measures. These measures were relative risk, hazard ratio, odds ratio, logistic coefficient, and mortality rate ratio. Studies that had complete raw data to facilitate calculations of the effect measures of interest were also included. Studies that only reported aggregate-level measures were excluded from this review.

Research type - Regarding types of publications, this review excluded commentaries, editorials, or letters to the editor based on publication type. As for the type of setting, there was no restriction on setting for inclusion in the review, however, hospital-based studies were taken note of during the extraction phase.

2.3 Abstract and full article screening

Abstracts were screened in pairs by CHAIN research assistants, using results from the search strategy presented above. Pairs needed to come to a common agreement for each abstract by applying the eligibility criteria outlined in table 1 below. In case of discrepancy, a third person was involved to make the final decision of inclusion or exclusion. During the abstract screening phase, articles that mentioned social group analysis were included because many studies may not explicitly state educational attainment as a measure examined, but rather state it as 'socioeconomic variables' instead. From the 31848 articles that went through this abstract screening phase, 3456 fit the inclusion criteria and were retained for the next phase, full text reading.

Table 1: Exclusion criteria for abstract screening

Criteria	Explanation of the exclusion criteria
Non-human	Non-human study
No mortality	Cervical cancer mortality or survival were not the outcome of interest in the study
All-cause mortality only	Reports only relative risks in all-cause mortality
No individual level	Data used are aggregated at local, regional, or national level- i.e., ecological study
No social group analysis	No comparison of mortality risk by social groups or own education. Terms referring to social group analysis

	include socioeconomic, socio-demographic, occupational, social, income and wealth inequalities/disparities, racial disparities/inequalities, poverty, education inequalities, migrant/native inequalities
No adults	The study does not include any individual of 18 years of age or older
Study design	Qualitative or case-crossover
Publication type	Commentary, editorial, letter, conference proceeding

Using a similar process as in the abstract screening phase, articles were fully read in pairs by CHAIN research assistants, using the criteria outlined in Table 2 below. During the full text reading phase, the presence of educational attainment as a measure in the analysis was determined. Articles were excluded if individual educational attainment was not present in the analysis. Articles were also evaluated for appropriateness of effect measures used, leading to the addition of ‘wrong effect measure’ in the exclusion criteria for the full text screening phase. From the 3456 articles that went through this full text screening phase, 455 were included and retained for the next phase of definition mapping. All research assistants received training prior to both the abstract and full article screening phases. The screening was completed using the online systematic review tool Rayyan.

Table 2: Exclusion criteria for full text reading

Criteria	Explanation of the exclusion criteria
Non-human	Non-human study
No mortality	Cervical cancer mortality or survival are not the outcome of interest in the study
All-cause mortality only	Reports only relative risks in all-cause mortality
No individual level	Data used are aggregated at local, regional, or national level.
No education	No comparison of mortality risk by education
Wrong effect measure	The effect measure is not RR, OR, HR, Logistic coefficient, or complete raw data not available
No adults	The study does not include any individual of 18 years of age or older
Study design	Ecological or case-crossover
Publication type	Commentary, editorial, letter

2.4 Definition mapping and extraction

This phase followed the full article screening and sought to outline and extract how cause of death was defined in each study, using the International Classification of Diseases (ICD) and the IHME Lancet Global Burden of Disease cause and risk summaries, as benchmarks. As this review was part of the global review on cause-specific adult mortality, relevant cervical cancer studies were found by identifying the cause-specific definitions and measures in each study. The International Classification of Diseases (ICD) is designed to promote international comparability in the collection, processing, classification, and presentation of mortality statistics (87). This includes providing a format for reporting causes of death on the death certificate. The ICD now has up to 11 revisions of global standards for recording health information and causes of death. Diseases are marked by codes of definition, for example, in ICD-10, cervical cancer is defined by the codes C53-C53.9, Z12.4, Z85.41 (87). Besides, the IHME Lancet Global Burden of Disease cause and risk summaries states that cervical cancer includes death and disability resulting from malignant neoplasms of the cervix, including ICD-10 codes such as C53 (88).

During this phase, studies that identified cervical cancer as a potential outcome were filtered. The definition extraction phase identified the following in each article; the cause of death list for potentially extractable causes, ICD round/revision (7, 8, 9, or 10) or an indication if that was not available, ICD definition (i.e. all ICD codes that apply to the cervical cancer definition in the study), extra codes of definition (i.e. ICD codes included in the study but not included in the IHME ICD codes), missing codes of definition (i.e. ICD codes of definition missing in the study compared to the IHME codes), descriptive/narrative definition only for studies that did not provide the exact ICD codes used, and finally the name of a mortality registry or source of cause of death when ICD codes were not defined or mentioned.

Two research assistants from CHAIN independently worked on the definition mapping and extractions using tables in Microsoft Excel. Studies reporting only ICD-7 or ICD-8 codes were extracted as so. In the case where studies used two revisions of the ICD, for example ICD-9 and ICD-10, the ICD codes of the latest round listed in the study were extracted. An initial evaluation of whether to include the article was taken during the definition landscape review. During this phase, studies that aggregated cervical cancer mortality with other causes of death were also identified and excluded. A reconciliation meeting with one additional reviewer from CHAIN was held upon completion of definition mapping to assess the accuracy of the extractions and reach a final agreement on inclusion or exclusion.

2.4.1 Additional exclusion criteria defined by IHME

Abstract and full article screening phases included studies that had cervical cancer survival as the outcome of interest. After the definition mapping phase, all studies that conducted a survival analysis of cervical cancer were excluded, as instructed by IHME.

2.5 Data extraction

All relevant data was extracted from articles that met the inclusion criteria during all prior phases (i.e., abstract screening, full text reading, and definition mapping) using a standardised extraction template in Microsoft Excel provided by IHME. The template included information such as, location (country or region); start and end date(s) of the study; age of participants; study design; absolute sample size; cohort-person years (if reported); duration of participant follow up (if relevant); method of measuring exposure (education) and outcome (cervical cancer mortality); cohort sample sizes for exposed and unexposed groups; effect measure estimates; an indication of whether or not the sample size of exposed and unexposed and total sample applied to the regression output/analysis, duration of follow-up; total death rate and death rate scale; educational groups definition according to study; and corresponding years of education, among others. If key information was missing from the article, for example sample sizes, these were consulted from population census datasets as indicated in the study. Confounders adjusted in the multivariate analysis were also extracted. ISCED-11 country specific mappings were used to determine corresponding numerical years of education for articles that reported only education categories. The extraction template also included information on the definition of the cause of death. The ICD codes of definition had to be extracted, as well as any extra or missing codes of definition. The researcher's extractions were cross-checked by one expert CHAIN reviewer to ensure the highest quality of data extraction.

2.6 Statistical procedures

2.6.1 Recalculation of effect sizes

Relative risk measures (MRR and RR) were chosen as the effect measure only for the meta-analysis of this review instead of odds ratios. This is because when there is no association between the exposure and outcome, relative risk and odds ratios are equal at 1, however, in the presence of an association between the exposure and outcome, odds ratios tend to overestimate the effect size compared to relative risk (89). Since studies have shown that education is associated with the risk of cervical cancer mortality, the odds ratios may overestimate the relationship. As such, effect sizes were recalculated for studies that used odds ratios (OR) as the effect measure. However, the qualitative synthesis of this study still incorporated the OR effect measures to facilitate examination of the association between educational attainment and mortality in a larger sample of the included studies than available for the meta-analysis.

Included studies reporting odds ratios were recalculated into the appropriate effect measures. Studies that contained raw data on both the number of cervical cancer deaths and population sizes for the unexposed and exposed groups were recalculated into RR using the formula below:

$$RR = \frac{\text{exposed deaths} / (\text{exposed deaths} + \text{exposed survivors})}{\text{unexposed deaths} / (\text{unexposed deaths} + \text{unexposed survivors})}$$

$$95\% \text{ CI} = \text{Ln} (RR) \pm 1.96 \frac{\sqrt{(n1-x1)/x1}}{n1} + \frac{\sqrt{(n2-x2)/x2}}{n2}$$

$$95\% \text{ CI for RR} = [e^{\text{lower CI}}, e^{\text{upper CI}}]$$

Included studies that reported mortality rates in person-years, as well as raw data on the total population sizes for the unexposed and exposed groups were recalculated into mortality rate ratios using the formulas below:

$$\text{MRR} = \frac{\text{Mortality rate exposed}}{\text{Mortality rate unexposed}}$$

The 95% CI for the recalculated MRR derived from these studies was found by calculating the total number of deaths and then the respective confidence intervals using the formulas below:

$$x_1 = \text{MR (exposed)} \times n_1$$

$$\frac{\quad}{100,000 \text{ person-years}}$$

$$x_2 = \text{MR (unexposed)} \times n_2$$

$$\frac{\quad}{100,000 \text{ person-years}}$$

$$95\% \text{ CI} = \text{Ln (MRR)} \pm 1.96 \left[\frac{\sqrt{(n_1 - x_1)/x_1}}{n_1} + \frac{\sqrt{(n_2 - x_2)/x_2}}{n_2} \right]$$

$$95\% \text{ CI for MRR} = [e^{\text{lower CI}}, e^{\text{upper CI}}]$$

2.6.2 Assessing Heterogeneity

Studies brought together in a systematic review will always differ, thus any kind of variability among them is termed heterogeneity. Variability in the participants, interventions and outcomes studied may be described as clinical heterogeneity, and variability in study design, outcome measurement tools and risk of bias may be described as methodological heterogeneity (84). Besides, variability in the intervention effects being evaluated in the different studies is known as statistical heterogeneity. Statistical heterogeneity manifests itself in the observed intervention effects being more different from each other than one would expect due to random error alone (84). As such, a test for heterogeneity was needed in this review. This was first done by using Cochran's Q test to assess the heterogeneity. Cochran's Q is defined as a weighted sum of squares; it uses the deviation of each study's observed effect from the summary effect, weighted by the inverse of the study's variance (90). A limitation of Cochran's Q test is that it might be underpowered when few studies have been included or when event rates are low, therefore, it is often recommended to adopt a higher p-value (rather than 0.05) as a threshold for statistical significance when using Cochran's Q test to determine statistical heterogeneity (91). Heterogeneity was then quantified using an I^2 statistic. The I^2 statistic indicates the percentage of the observed variability in the effect sizes due to between-study (statistical)

heterogeneity rather than chance alone (84). However, it is important to note that the importance of the observed value of I^2 depends on the magnitude and direction of effects, and the strength of evidence for heterogeneity (e.g., a confidence interval for I^2 : uncertainty in the value of I^2 is substantial when the number of studies is small (90). As such, interpretation of the I^2 statistic can be misleading since the importance of inconsistency depends on several factors. The degree of heterogeneity in the I^2 statistic was therefore determined as being low (0-25%), medium (25-75%), or high (75-100%) (90).

A random-effects model was chosen a priori for the meta-analysis because it upholds the notion that it is implausible that the intervention effect (i.e., The effect of educational attainment on cervical cancer mortality) is identical across all studies (unless the intervention has no effect at all) (84). The random effects model incorporates an assumption that the different studies are estimating different, yet related, intervention effects, and therefore allows for heterogeneity to be addressed (84).

2.6.3 Stratified Analyses

A stratified meta-analysis according to age and region was completed with the intent to explore the variations in the possible association of educational attainment and cervical cancer mortality.

2.6.4 Publication Bias

Funnel plots are usually used to inspect small-study effects. A funnel plot is a scatter plot of the studies' observed effect sizes on the x-axis against a measure of their standard error on the y-axis (90). The y-axis in funnel plots is usually inverted, meaning higher values on the y-axis represent lower standard errors. When there is no publication bias, the data points in such a plot should form a roughly symmetrical, upside-down funnel (90). The use of funnel plots was not feasible in our study because these plots are only appropriate for detecting publication bias when studies included in the meta-analysis come from one underlying population, which was not the case for the studies we included (92).

2.6.5 Software

Statistical analyses were completed using RStudio with R version 4.0.3 (93). The dmetar package version 0.0.9000 developed for R was utilised to compute overall effect sizes, p-values, I^2 values, confidence intervals, forest plots, bar plots, and stratified analyses.

2.7 Ethical Considerations

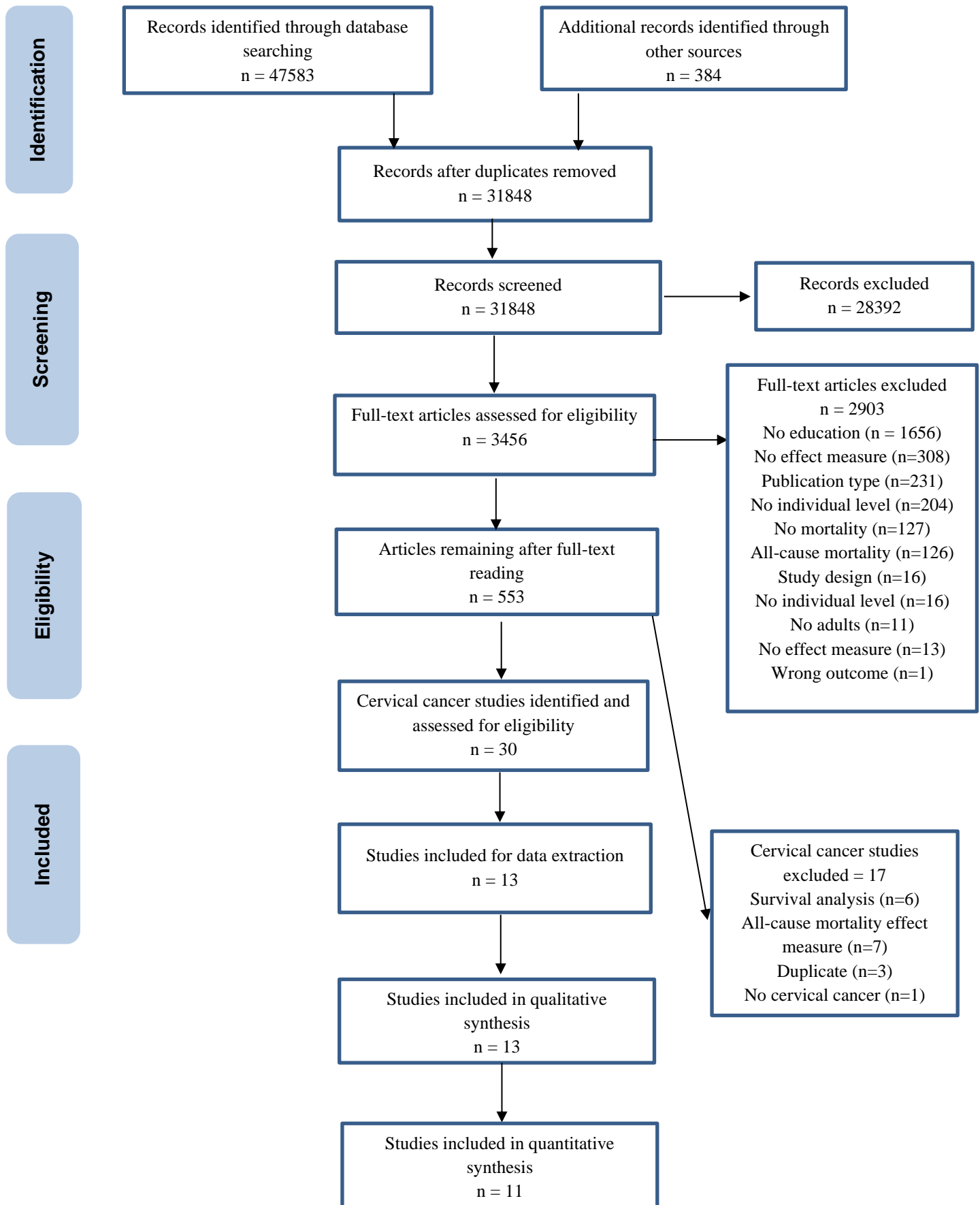
Ethical approval was not required for this study as data retrieved and analysed from the search strategy constituted previously published works. While this project does not require ethical approval, the methodological nature of systematic reviews and meta-analyses can influence policy, thus the ethical responsibility lies in the quality of the data obtained as well as the conclusions that are drawn.

3.0 Results

After duplicate removal, 15,345 records were finally selected for abstract screening. Of these, 14,961 were detected from searched databases and 384 were yielded by the snowball hand search of systematic reviews and meta-analysis. The abstract screening phase led to the identification of 1,749 papers for full reading. Absence of cause-specific mortality or social group analyses were the main reasons for exclusion during the abstract phase. During the full reading phase, the absence of education was the main reason for exclusion. Besides, only studies of adults 18 years old or older were included, however exceptions were made for 8 studies that included only a small group below the threshold. The full reading phase led to the identification of 553 included articles. The cause of death list for potentially extractable causes was then identified for each study. A total of 30 studies that had cervical cancer as the outcome of interest were filtered through this process. Following this, a quality check was conducted for each study to see if in fact cervical cancer was an extractable effect measure outcome that was ICD coded, coming from a registry, or a case identified through a hospital-based study.

Of the 30 studies, 13 were included for the final data extraction phase. The main reason for exclusion during this phase was the inability to extract an effect measure relating to level of education and cervical cancer only (7 studies), as well as survival being the outcome of interest, as opposed to mortality (6 studies). The PRISMA flow diagram below summarises the research process from search query to extraction. Of the 13 studies included in this review's analysis, 11 were retrospective cohort studies and 2 were prospective cohort studies. Across the retrospective cohort studies, 6 reported the total cohort person-years of follow-up which was a total of 90,905,473. Besides, 8 reported the total cohort sample size which was a total of 172,689,182. Of these total cohort sample sizes, 10 applied to the regression output/analysis. One study from Slovenia included women under the age of 18, but the extracted sample sizes were only for women over the age of 15. Across the prospective cohort studies, only one based in France reported total cohort sample size (65,291), and the other based in Spain, reported total cohort person-years at risk (102,265,757). The total death rate scale was reported in only 6 studies. One study based in Sweden reported this per 10,000 person-years (19.4 for those with low education and 10.1 for those with medium education). The rest reported death rates per 100,000 person-years (2.7 at the lowest in the United States among a non-Hispanic white group with low and medium education, and 19.4 at the highest in Sweden among those with low education).

Figure 2: PRISMA flow diagram



3.1 Quality assessment of articles

All included studies were appraised using the Joanna Briggs Institute (JBI) critical appraisal checklist for cohort studies. This was done to determine the extent to which studies addressed the issue of bias in design, conduct, and analysis. The researcher independently applied the checklist to the articles and the results were assessed by a second reviewer. Studies were categorised as “fair” “good” and “excellent” **Appendix 2** provides further details on the total scores associated with each level of categorization. The appraisal checklist had the ‘yes’ answer equating to 1 point and ‘no’, ‘unclear’ and ‘not applicable’ equating to 0 points. There were 9 studies of excellent quality and 4 of good quality (69% and 31% respectively). No study was found to be of fair quality. Across the cohort studies, the lack of identification and controlling of confounding factors was a common reason for lower scoring.

3.2 Study characteristics

Almost all the included studies (92%) were conducted in high-income country settings, particularly in Europe, apart from one study which was conducted in Colombia, an upper-middle income country. Majority of the studies were representative of the entire population (10), and the 3 studies that were not representative of the entire population included studies that only captured data for specific racial groups in selected geographical locations of the United States, as well as data for specific cities (Barcelona and Madrid). Table 3 below summarises these study settings.

Table 3: Study settings

Country	N = 13
Spain	3
Lithuania	2
Slovenia	1
Sweden	1
France	1
United States of America	2
Norway	1
Colombia	1
Italy	1

Regarding the measurement of exposures, all studies used administrative registries, mainly population census, thus only observed at the baseline. Population census data was then linked to outcomes of interest in the study to facilitate the analysis. As for the measurement of the outcome of interest, all studies used administrative registries, such as cancer registries in

tandem with mortality registries, to determine cervical cancer mortality. Three studies also used death certificates as an additional measure of the outcome. Since the type of follow up measure was not indicated in all the studies, it was extracted as maximum. The length of follow-up for the cohort studies, on the other hand, ranged from 6 months to 19 years. By the nature of the outcome of interest in this study, there were no male individuals included in the analysis. Most studies had the youngest person aged 25 years old (54%). Only one study based in Slovenia also included participants below the age of 18. The age of the oldest participant was also specified for most studies, except for three studies where the age end was extracted as 99. Table 4 below gives an overview of the descriptive characteristics of the included studies.

Table 4: Descriptive characteristics of included studies

Author	Study source	Study design	Cohort person-years (sub-group definition)	Cohort sample size (sub-group definition)	Years follow-up	Total death rate	Death rate scale (person-years)
Fernandez & Borrell (1999)	1992-1995 Barcelona Mortality Registry and 1991 Barcelona Municipal Census	Retrospective cohort	2424884	6797	4	n.d.	n.d.
Jasilionis et al., (2015)	2001 population census	Retrospective cohort	52414303	1128798	8.8	n.d.	n.d.
Smailyte et al., (2012)	2001 population census, Statistics Lithuania, and the Lithuanian Cancer Registry	Retrospective cohort	2963514	n.d.	3.5	n.d.	n.d.
Martínez et al., (2009)	2001 population census of the region of Madrid (Spain) and linked mortality registry	Retrospective cohort	1527629 (Women aged 25-44) 1067989 (Women aged 45-64)	n.d. n.d.	1.7	n.d.	n.d.
Simon et al., (2012)	Registry of deaths database of the residents of Slovenia, National	Retrospective cohort	n.d. n.d.	877029 (Women aged 0 to 84) 683864	5	n.d.	n.d.

	Institute of Public Health (NIPH)			(Women aged 0 to 64)				
Li et al., (2012)	National Registry of Causes of Death; Swedish Cancer Registry	Retrospective cohort	n.d.	1887118	19	29.5	10,000	
Menvielle et al., (2005)	Echantillon Demographique Permanent (EDP)	Prospective cohort	n.d.	65291	16	n.d.	n.d.	
Singh & Jemal (2017)	The national mortality database, the 1979–2011 National Longitudinal Mortality Study (NLMS), and the SEER cancer registry database	Retrospective cohort	n.d.	1972681 (Women 1979-1998)	19	25.28	100,000	
				1088128 (Women 2003-2011)	8			
Elstad et al., (2011)	Norwegian linked national registries, Statistics Norway	Retrospective cohort	5929209 (Women 1971-1979)	n.d.	8	38	100,000	
				6360249 (women 1980-1989)	n.d.			9
				8775799 (Women 1990-2002)	n.d.			12
Vries et al., (2015)	Colombian National Mortality data linked to national census	Retrospective cohort	n.d.	93567472	10	16.55	100,000	
Simard et al., (2012)	National Vital Statistics System and linked census data	Retrospective cohort	n.d.	33709707	3	22.9	100,000	

Reques et al., (2014)	National Institute of Statistics Spain, census dataset linked to population and mortality registries.	Prospective cohort	102265757	n.d.	7.2	3.4	100,000
Faggiano et al., (1995)	1981 Italian population census linked to national death index	Retrospective cohort study	9441897	18883794	0.5	n.d.	n.d.
				12980605 (women in Northern and Central regions)	n.d.	n.d.	n.d.
				5903189 (women in Southern region)	n.d.	n.d.	n.d.

As for definitions of the cause of death, majority of the studies (69%) used the ICD-10, with C53 as the only code of definition, no extra codes of definition, and Z12.4, Z85.41 as the missing codes of definition. 23% of the studies used ICD-9, with 180 as the common code of definition and V10.41, V72.32 as the missing codes of definition. Of these, one study included the ICD-9 codes 179, 181, and 182 as the extra codes of definition. One study used both ICD 9 and 10 codes of definition according to the year of interest in the sub-group analysis (1993-1995 and 2003-2005, respectively). It should be noted that the specified “missing codes of definition” from these studies, are codes that exist to increase the accuracy of case definitions when there is missing information. Table 5 below summarizes the cervical cancer definitions for all included studies.

Table 5: Cervical cancer definitions for included studies

Study	ICD round	ICD definition	Extra codes of definition	Missing codes of definition
Fernandez & Borrell (1999)	9	180	N/A	V10.41, V72.32
Jasilionis et al., (2015)	10	C53	N/A	Z12.4, Z85.41
Smailyte et al., (2012)	10	C53	N/A	Z12.4, Z85.41
Martínez et al., (2009)	10	C53	N/A	Z12.4, Z85.41
Simon et al., (2012)	10	C53	N/A	Z12.4, Z85.41

Li et al., (2012)	10	C53	N/A	Z12.4, Z85.41
Menvielle et al., (2005)	9	180	179, 182	V10.41, V72.32
Singh & Jemal (2017)	10	C53	N/A	Z12.4, Z85.41
Elstad et al., (2011)	10	C53	N/A	Z12.4, Z85.41
Vries et al., (2015)	10	C53	N/A	Z12.4, Z85.41
Simard et al., (2012)	10	C53	N/A	Z12.4, Z85.41
	9	180	N/A	V10.41, V72.32
Reques et al., (2014)	10	C53	N/A	Z12.4, Z85.41
Faggiano et al., (1995)	9	180	179, 181, 182	V10.41, V72.32

3.3 Educational attainment and cervical cancer mortality: Qualitative synthesis

All the 13 studies included in this study presented effect sizes for the entire study population which are recorded in table 4 below. For this synthesis, the effect sizes comparing the lowest educational group with the highest educational group in respective studies have been reported. It should be noted that the educational categories used by the studies, and therefore the corresponding years of education, vary by study, thus comparison between studies is impossible. Most studies (77%) suggested an association between low level of education and higher cervical cancer mortality. In one study, Simard et al. 2012, this association was not evident for only one sub-group analysis (Hispanics; year 2005-2007). While the study by Li et al., (2012) suggested no association between low level of education and higher cervical cancer mortality, one sub-group analysis further suggested that those with a lower level of education were 2% less likely to die from cervical cancer compared to those with a higher level of education(OR=0.98).

Table 6: Reported effect sizes for included cohort studies

Study	Effect size (effect measure)	CI	Ages	Representative (country or specified)/sub-group analysis	Covariates	Education groups compared	Country
Fernandez & Borrell (1999)	2.62 (RR)	[1.09-6.27]	25+	Barcelona; females	Age at death in decades	≤4yrs. vs. 15≥25yrs. (ref)	Spain
Jasilionis et al., (2015)	3.37 (MRR)	[2.73-4.16]	30-84	Females	Age	≤9yrs. vs. 14≥25yrs. (ref)	Lithuania
Smailyte et al., (2012)	2.74 (MRR)	[1.99-3.75]	40-79	Females	None	≤9yrs. vs. 14≥25yrs. (ref)	Lithuania

Martínez et al., (2009)	1.60 (MRR)	n.d.	25-44	Madrid	None	≤6yrs. vs. 10≥25 yrs. (ref)	Spain
	1.43 (MRR)	n.d.	45-64	Madrid	None	≤6yrs. vs. 10≥25 yrs. (ref)	
Simon et al., (2012)	2.08 (MRR)	[1.31-3.57]	0-84	✓	None	≤6yrs. vs. 16≥23yrs. (ref)	Slovenia
	1.99 (MRR)	[1.22-3.67]	0-64	✓	None	≤6yrs. vs. 16≥23yrs. (ref)	
Li et al., (2012)	0.98 (OR)	[0.81-1.18]	25-74	✓	Age, marital status, country of birth, area of residence, parity, family income, educational attainment, mobility, number of partners	≤9 yrs. vs. 12≥25 yrs. (ref)	Sweden
	1.02 (OR)	[0.85-1.23]	25-74	✓	Age, marital status, country of birth, area of residence, parity, family income, educational attainment, mobility, number of partners, hospitalization for disease	≤9 yrs. vs. 12≥25 yrs. (ref)	
Menvielle et al., (2005)	1.9 (RR)	[1.0-3.6]	35-59	Females	None	≤4yrs. vs. 12≥20yrs. (ref)	France
Singh & Jemal (2017)	2.49 (RR)		25+	Females; 1979-1998	None	≤12yrs. vs. 16≥25yrs. (ref)	United States of America
	6.25 (RR)		25+	Females; 2003-2011	None	≤12yrs. vs. 16≥25yrs. (ref)	

Elstad et al., (2011)	2.03 (OR)	[1.36-3.01]	45-74	Females; 1971-1979	None	≤9yrs. vs. 13≥25yrs. (ref)	Norway
	2.87 (OR)	[1.90-4.30]	45-74	Females; 1980-1989	None	≤9yrs. vs. 13≥25yrs. (ref)	
	1.98 (OR)	[1.55-2.54]	45-74	Females; 1990-2002	None	≤9yrs. vs. 13≥25yrs. (ref)	
Vries et al., (2015)	5.75 (RR)	[5.05-6.54]	25-64	Females	None	≤5yrs. vs. 12≥22yrs.	Colombia
Simard et al., (2012)	3.1 (RR)	[2.4-3.9]	25-64	Non-hispanic white; year (1993-1995)	None	≤12yrs. vs. 16≥25yrs. (ref)	United States of America
	4.4 (RR)	[3.5-5.6]	25-64	Non-hispanic white; year (2005-2007)	None	≤12yrs. vs. 16≥25yrs. (ref)	
	3.8 (RR)	[2.0-7.0]	26-64	Non-hispanic black; year (1993-1995)	None	≤12yrs. vs. 16≥25yrs. (ref)	
	5.6 (RR)	[3.1-10.0]	25-64	Non-hispanic black; year (2005-2007)	None	≤12yrs. vs. 16≥25yrs. (ref)	
	2.5 (RR)	[0.8-8.5]	25-64	Hispanic; year (2005-2007)	None	≤12yrs. vs. 16≥25yrs. (ref)	
Reques et al., (2014)	2.11 (MRR)	[1.82-2.45]	25+	Females	None	≤6yrs. vs. 14≥22yrs.	Spain
Faggiano et al., (1995)	1.76 (RR)	[1.23-2.5]	18-74	Females	Age, area of residence	0 yrs. vs. 11≥13 yrs.	Italy
	1.33 (RR)	n.d.	18-74	Females; North	Age, area of residence	0 yrs. vs. 11≥25 yrs.	Italy
	1.44 (RR)	n.d.	18-74	Females; Centre	Age, area of residence	0 yrs. vs. 11≥25 yrs.	Italy
	4.28 (RR)	n.d.	18-74	Females; South	Age, area of residence	0 yrs. vs. 11≥25 yrs.	Italy

Note: Studies coloured in yellow suggested no/unclear association between level of educational attainment and cervical cancer mortality as the confidence intervals included the null value of 1

3.4 Educational attainment and cervical cancer mortality: Meta-analysis

In this review, education was understood as the highest educational attainment of an individual, measured by both numbers of years of schooling and educational level achieved. The use of the ISCED enabled the country-specific transformation of education levels into years of education. This is due to ISCED's provision of a framework that organises education programmes and related qualifications by levels and the years of education they account for. The ISCED recognizes 8 different educational levels with the following years of education (94); **ISCED 0**: no duration criteria, **ISCED 1**: 4 to 7 years, **ISCED 2**: 2 to 5 years, **ISCED 3**: 2 to 5 years, **ISCED 4**: 6 months to 2 or 3 years, **ISCED 5**: 2 to 3 years, **ISCED 8**: minimum of 8 years. **ISCED 6** varies from 3 to 4 or more years when directly following ISCED level 3, or 1 to 2 years when following another ISCED 6 programme. Lastly, **ISCED 7** varies from 1 to 4 years when following ISCED level 6, or 5 to 7 years when directly following ISCED level 3. Based on this, years of education for each study were further grouped into "low" "medium" and "high" categories; low education (ISCED levels 0-2), medium education (ISCED levels 3-4), and high education (ISCED levels 5-8), as shown in table 5 below (95). As indicated in table 5, some studies had more than one "low" and "medium" categorisation. Thus, an average of the effect sizes relating to the same education category was found. The confidence interval constituted of the lowest lower limit and highest upper limit of the respective effect sizes.

Studies by Li et al., (2012) and Elstad et al., (2011) had reported effect sizes using OR, thus effect sizes were recalculated into relative risk measures (MRR and RR) using each study's available raw data. Besides, the study by Elstad et al., (2011) had raw data available for the years 1971-1979; 1980-1989; and 1990-2002. Effect size recalculation was only conducted for the latter year group for the meta-analysis to facilitate analysis among other studies which did not date as far back as the 70's and 80's. Two studies were excluded because they did not include a 95% CI for the effect sizes, despite reporting with the effect measure of interest. As such, the primary factors for inclusion into the meta-analysis were (1) the possibility to reclassify the study's educational attainment into 'low' 'medium' and 'high' categories, (2) the study reporting an appropriate effect size measure with a degree of uncertainty (in this case a 95% CI), (3) the availability of adequate information to recalculate the effect size to the appropriate measure with a 95% CI.

Table 7: Recategorization of education level for meta-analysis

Study	Country	ISCED grouping	Education definition	Approx. years of education	Education classification
Fernandez & Borrell (1999)	Spain	0-2	Less than primary	0 to 4	Low
		0-2	Primary	5	Low
		3-4	Middle school	8	Medium
			High school	11 to 14	Medium
		5-8	University	15 to 25	High (ref.)

Jasilionis et al., (2015)	Lithuania	0-2	Lower than secondary	0 to 9	Low
		3-4	Secondary	10 to 13	Medium
		5-8	Higher	14 to 25	High (ref.)
Smailyte et al., (2012)	Lithuania	0-2	Lower than secondary	0 to 9	Low
		3-4	Secondary	10 to 13	Medium
		5-8	Higher	14 to 25	High (ref.)
Martinez et al., (2009)	Spain	0-2	First level or no education	0 to 6	Low
		3-4	Second level, first cycle	9	Medium
		5-8	Second level, second cycle	10 to 25	High (ref.)
Simon et al., (2012)	Slovenia	0-2	Low - primary school or less	0 to 6	Low
		3-4			
		5-8	High - higher education level and all subsequent levels	16 to 23	High (ref.)
Li et al., (2012)	Sweden	0-2	Compulsory school or less	0 to 9	Low
		3-4	Practical high school or some theoretical high school	10 to 11	Medium
		5-8	Theoretical high school and/or college	12 to 25	High (ref.)
Menvielle et al., (2005)	France	0-2	Incomplete elementary education	0 to 4	Low
		0-2	General elementary education	5	Low
		3-4	Vocational education (and secondary and intermediate general)	9 to 11	Medium
		5-8	High school and higher education	12 to 20	High (ref.)
Singh & Jemal (2017)	United States of America	0-2			

		3-4		12 & 13 to 15	Medium
		5-8		16 to 25	High (ref.)
Elstad et al., (2011)	Norway	0-2	Basic	0 to 9	Low
		3-4	Secondary	10 to 12	Medium
		5-8	Tertiary	13 to 25	High (ref.)
Vries et al., (2015) RR	Colombia	0-2	Primary or less	0 to 5	Low
		3-4	Secondary	6 to 11	Medium
		5-8	Tertiary	12 to 22	High (ref.)
Simard et al., (2012)	United States of America	0-2 & 3-4		0 to 12	Low
		5-8		16 to 25	High
Reques et al., (2014)	Spain	0-2	primary level or less (ISCED 1)	0 to 6	Low
		3-4			
		5-8	University, tertiary education (ISCED 5 and 6)	14 to 22	High (ref.)
Faggiano et al., (1995)	Italy	0-2	Illiterate	0	Low
		0-2	Barely illiterate	1-4	Low
		0-2	Primary	5	Low
		3-4	Middle school	8	Medium
		5-8	High school	12 to 13	High (ref.)

Note: Studies coloured in red did not meet the inclusion criteria for the meta-analysis of this review

3.5 Results of the meta-analysis

A total of 11 studies allowed for the meta-analysis for level of education and cervical cancer mortality. Figure 3 shows the risk of mortality for those with low level of education, with high level of education as the reference group. The risk ratios (RR) and 95% confidence intervals, along with the log (RR) and standard error of the log (RR) have been visualized using a forest plot. Respective weights for the random-effects model have also been depicted.

The size of the squares represents the amount of weight the study placed on the overall effect estimation, with smaller squares indicating a small weight, large uncertainty (denoted by the wide confidence interval), and a high standard error. On the other hand, the larger squares have the largest weight, a low standard error, and small uncertainty (denoted by a narrow confidence interval that is white in colour as opposed to the standard black colour). The null value of 1 entails that there is no additional risk of cervical cancer mortality for those with low level of

education compared to those with a high level of education. As such, if an estimate's confidence interval includes the value of 1, the association between these two educational groups is non-significant, because the confidence interval indicates where the true population risk would lie, assuming no confounding or bias, with 95% certainty. Based on this interpretation, the farther the squares in the forest lie to the right of the null-value-of-1 line, the greater the effect, and thus a greater risk of cervical cancer mortality due to low level of education. Conversely, the squares that lie to the left of the null-value-of-1 line indicate a smaller effect and thus, a smaller risk of cervical cancer mortality due to low level of education.

In the analysis depicted in figure 3 below, the risk ratios ranged from 1.40 to 5.75. Of these, only 4 studies had estimates that included the null value of 1 (Fernandez & Borrell 1999, Menvielle et al., 2005, Faggiano et al., 1995, and Simard et al., 2012). The overall estimate effect calculated using the random-effects model indicated a risk ratio of 2.41, indicating that individuals with low education have a greater risk of cervical cancer mortality compared to those with a high level of education. The confidence interval of the overall estimate, 95% CI of 1.81 to 3.20, showed a statistically significant effect of this association $z = 6.06$, $p < 0.01$. A risk ratio of 2.41 entails that the risk of cervical cancer mortality is 141% higher among those with a low level of education compared to those with a high level of education. To assess heterogeneity, the Q statistic was statistically significant ($Q=213.15$, $p < 0.01$) and the I^2 value estimates that 95% of the variation across the studies was due to significant heterogeneity, and not chance.

Figure 3: Forest plot for low education vs. high education

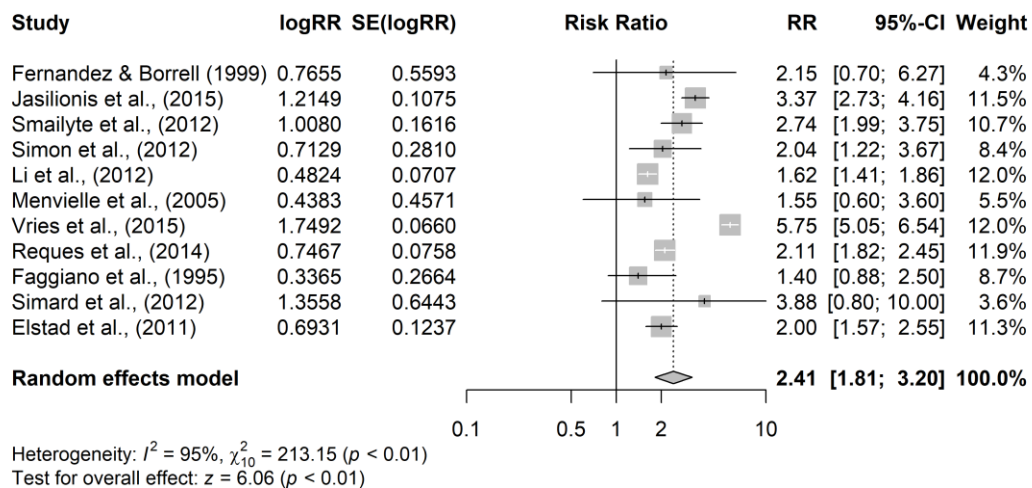
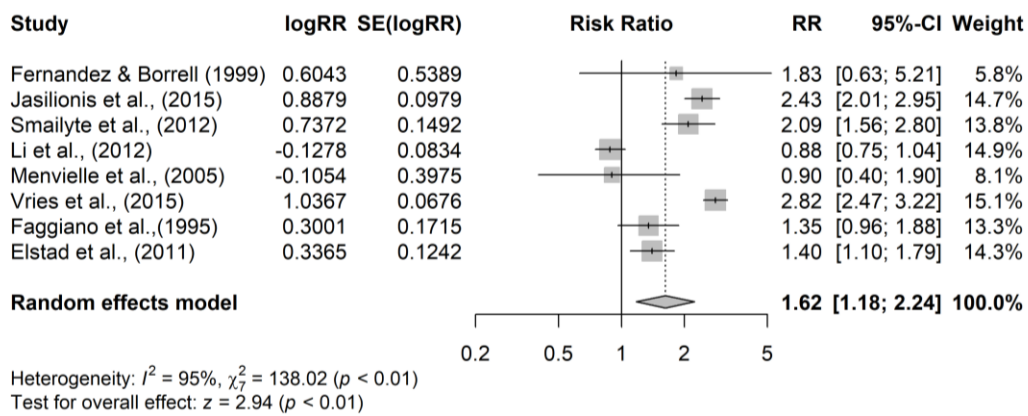


Figure 4 below shows the risk of mortality for those with medium level of education, with high level of education as the reference group. Eight studies were used in this analysis due to the availability of information on the respective education groups and their related effect sizes. The risk ratios (RR) and 95% confidence intervals, along with the log (RR) and standard error of

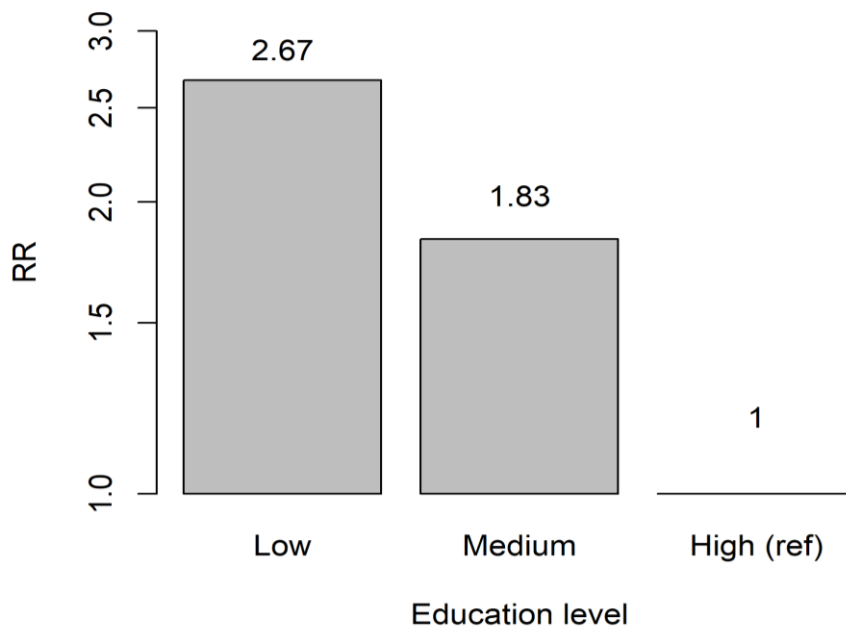
the log (RR) have been visualized using a forest plot. Respective weights for the random-effects model have also been depicted. In this analysis, the number of studies with estimates that included the null value of 1 in the confidence interval versus those that did not, was equal. Despite this, the overall estimate effect still indicated a risk ratio of 1.62 which suggests that those with medium education have a 62% higher risk of cervical mortality compared to those with high level of education (95% CI of 1.18 to 2.24 and $z = 2.94$, $p < 0.01$). Again, the assessment for heterogeneity suggests that 95% of the variation across studies was due to significant heterogeneity and not chance ($Q = 138.02$, $p < 0.01$).

Figure 4: Forest plot for medium education vs. high education



It is important to note the significant gap in the risk of cervical cancer mortality between those with low level of education and those with medium level of education, when compared to those with a high level of education. Thus far, we see that those with a low level of education (ISCED 0-2) have almost twice the risk of cervical cancer mortality than those with medium level of education (ISCED 3-4) when compared to those with high level of education (ISCED 5 and above). Figure 5 below depicts this educational gradient in cervical cancer mortality.

Figure 5: Educational gradient in cervical cancer mortality



3.5.1 Stratified analysis by region

A stratified analysis was conducted to explore how the association between level of education and cervical cancer mortality varies according to region. Since majority of the included studies were based in Europe, the stratification was done for Northern and Southern Europe. These regions were also selected based on the number of studies available for geographical representation within specific regions. Figure 6 below shows the risk of cervical mortality among those with low level of education, with the high level of education as the reference group, for each regional stratum. Both strata show a significant increase in the risk of cervical cancer mortality. Those in the South had 1.93 times the risk ($z=4.48$, $p<0.01$) while those in the North had 1.76 times the risk ($z=5.50$, $p<0.01$). However, the test for differences between the strata showed that the difference in the risk of cervical cancer mortality was not statistically significant ($X^2=0.27$, $p=0.60$). The Q statistic was not statistically significant in both the North ($Q=2.19$, $p=0.14$) and South ($Q=2.2$, $p=0.33$). Besides, the I^2 value suggested medium heterogeneity in the North (54%) and low heterogeneity in the South (9%). For the overall random effects model, the Q statistic was statistically significant ($Q=8.09$, $p=0.09$), and the I^2 value suggested medium heterogeneity (51%).

Figure 6: Forest plot for low education vs. high education by region

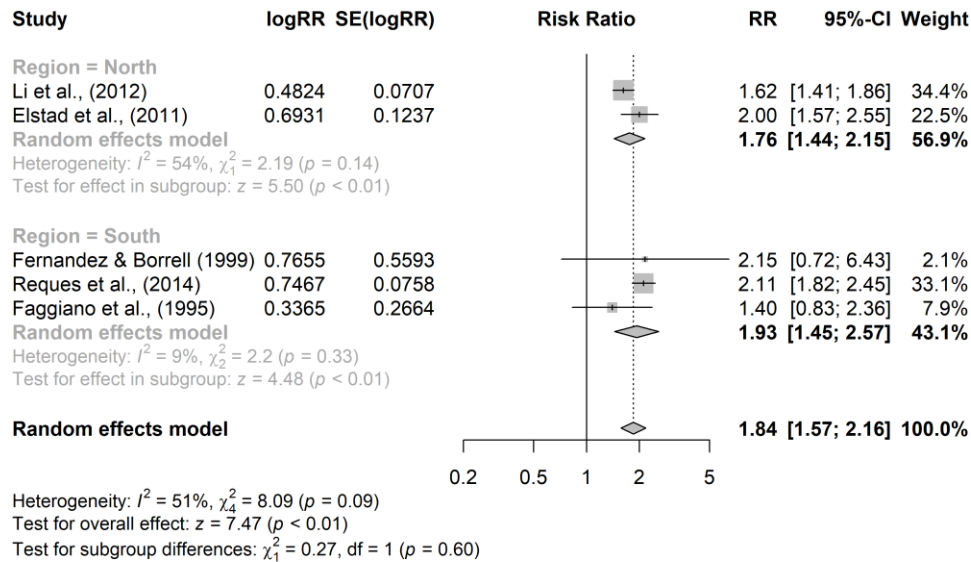
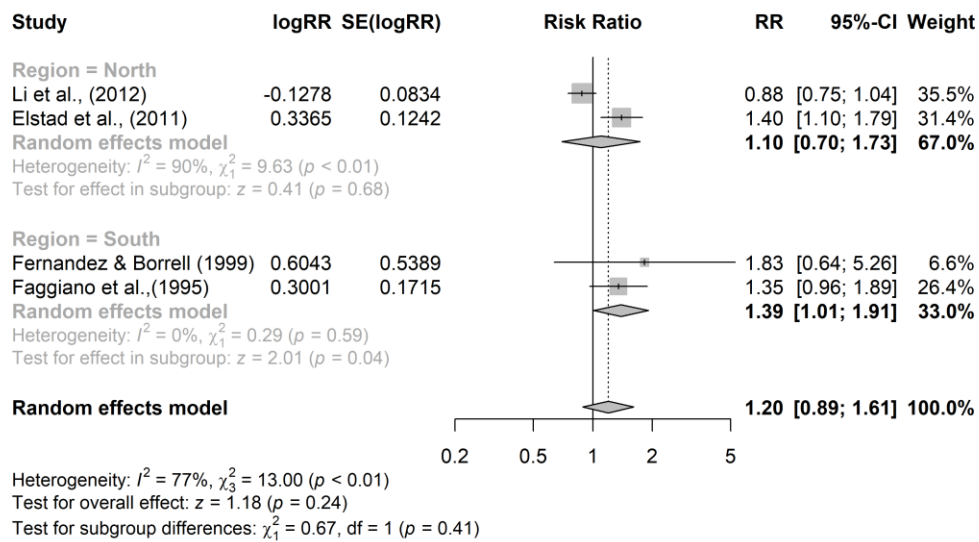


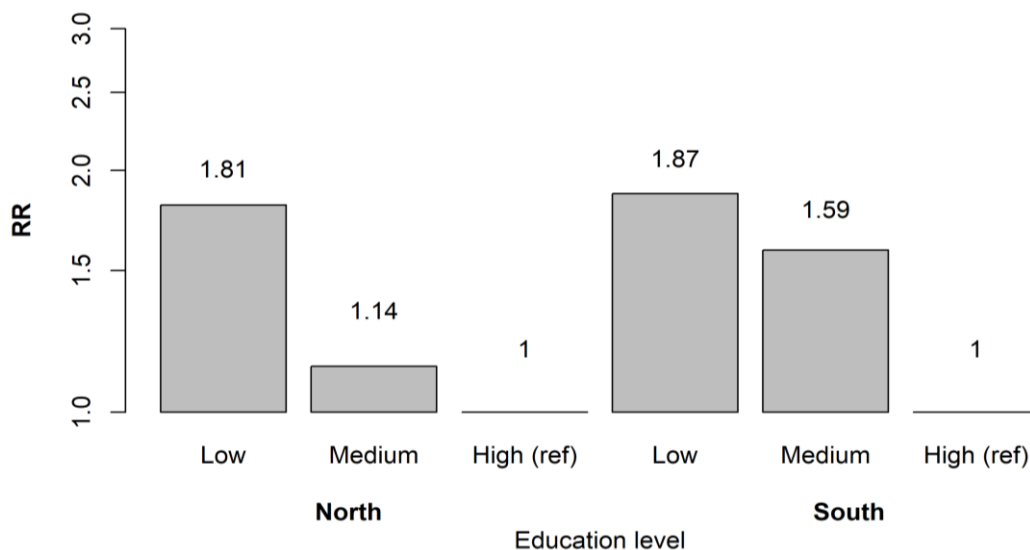
Figure 7 below shows the risk of cervical mortality among those with medium level of education, with the high level of education as the reference group, for each regional stratum. The North strata shows a non-significant increase in the risk of cervical cancer mortality ($z=0.41$, $p=0.68$), while the South shows a significant increase ($z=2.01$, $p=0.04$). In comparison to the previous analysis (between the low and high education level groups) we find that the *p-value* for the increase in the risk of cervical cancer mortality has increased in this analysis, more prominently in the North than the South as well. It is also imperative to note that the Q statistic was only statistically significant in the North ($Q=9.63$, $p<0.01$) and statistically non-significant in the South ($Q=0.29$, $p=0.59$). Besides, the I^2 value in the North suggested high heterogeneity (90%) and low heterogeneity in the South (0%). While those in the North had 1.10 times the risk of cervical cancer mortality and those in the South had 1.39 times the risk, the test for differences between the strata showed a statistically non-significant difference between the two regions ($X^2=0.67$, $p=0.41$). The Q statistic for the overall random effects model was statistically significant ($Q=13.00$, $p<0.01$) and the I^2 value suggested medium heterogeneity (77%).

Figure 7: Forest plot for medium education vs. high education by region



In figure 8, the educational gradient in cervical cancer mortality for both Northern and Southern Europe has been depicted. It is observed that the mortality gradient is much steeper in the North than it is in the South when we consider the influence of an additional year of education on the risk of cervical cancer mortality. That is, an additional level of education sharply reduces the risk of cervical cancer mortality in the North than it does in the South. Based on this, it can be argued that women in the South with a low level of education experience a higher increased risk of mortality, compared to women in the North, if they do not attain an additional level of education. This is considering the evidence shown that the risk of cervical cancer mortality for those with low education when compared to those with high education does not differ too strikingly between the two regions.

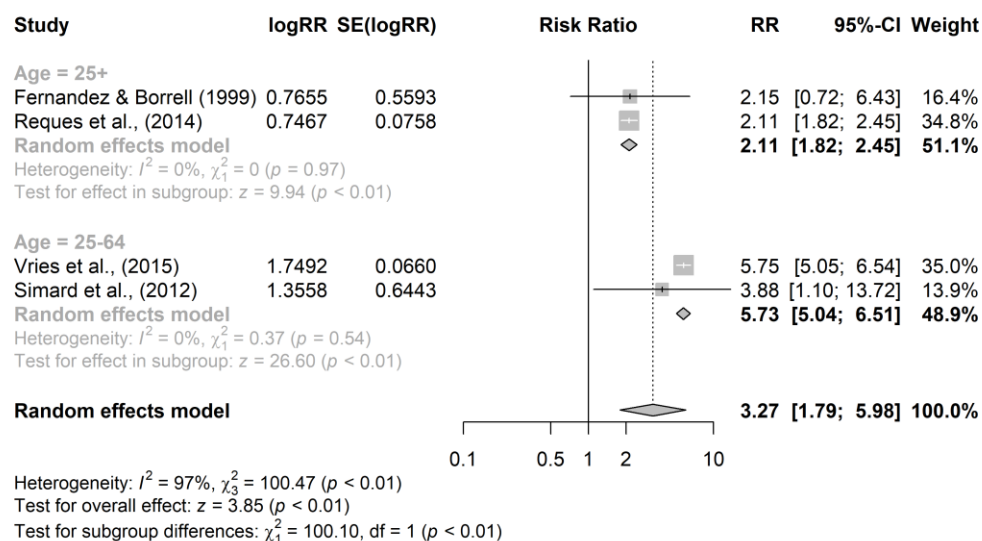
Figure 8: Educational gradient in cervical cancer mortality by region



3.5.2 Stratified analysis by age

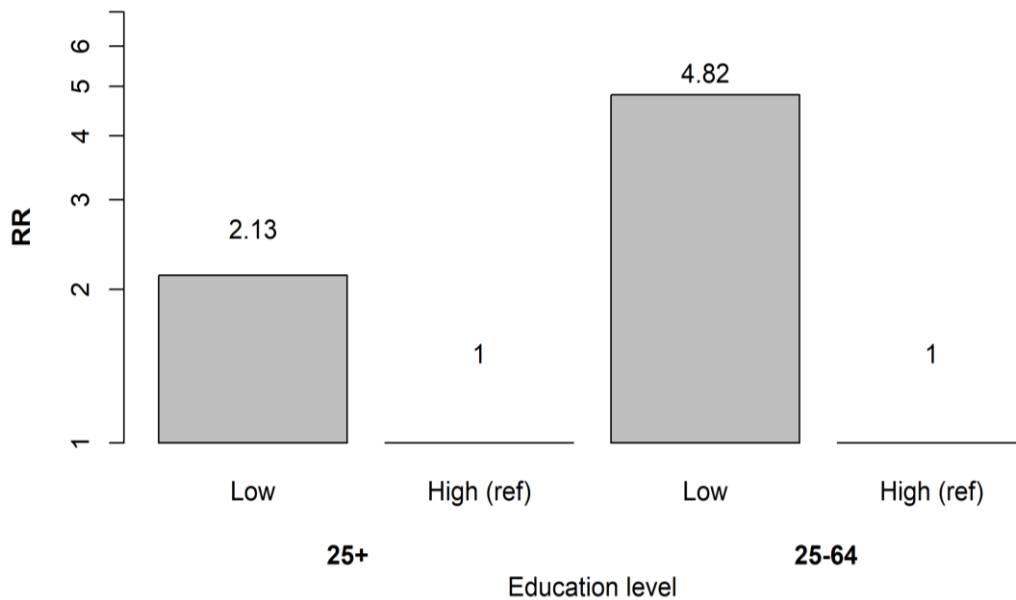
A stratified meta-analysis according to age was completed using four studies. Due to the availability of information on effect sizes for educational groups according to age, the analysis was only possible for the low vs. high education level comparison. Figure 9 below shows the forest plot for two age strata, age groups 25-64, and 25+. Both age groups show a significant increase in the risk of cervical cancer mortality, with equal *p-value* ($p < 0.01$). However, the 25-64 age group was found to have 5.73 times the risk of cervical cancer mortality, while the 25+ age group had 2.11 times the risk of mortality. Besides, the test for sub-group differences was statistically significant ($Q=100$, $p < 0.01$). In the overall random effects model, the *Q* statistic suggested statistically significant heterogeneity ($Q=100.47$, $p < 0.01$), and the I^2 value was 97% suggesting high heterogeneity. However, the *Q* statistic was not statistically significant in either the 25+ stratum ($Q=0$, $p=0.97$), or the 25-64 stratum ($Q=0.37$, $p=0.54$), with an I^2 value of 0% in both suggesting low heterogeneity.

Figure 9: Forest plot for low education vs. high education by age



Finally, figure 10 depicts the educational gradient in mortality for the two age groups. The younger age group has a very steep gradient, with a risk of cervical cancer mortality that is more than twice that of the older age group. While the increased risk of cervical cancer mortality between the two strata is evidenced, the disparity is striking. This calls to attention the importance and impact educational attainment have on younger populations, as opposed to older populations across the lifespan.

Figure 10: Educational gradient in cervical cancer mortality by age



4.0 Discussion

The findings of this systematic review and meta-analysis support our hypothesis that lower educational attainment is associated with increased cervical cancer mortality. Although clear pathways of association between level of education and cervical cancer mortality could not be explicitly observed, education as a social determinant of health is clearly evidenced. Drawing back, for example, to the social causation theory and the fundamental cause theory, we find that education is a socioeconomic status indicator that increases people's access to and awareness of health services, as well as their potential to adopt health-seeking behaviours such as cancer screening. A systematic review and meta-analysis on the impact of level of education on adherence to breast and cervical cancer screening further puts this into perspective as it found that women with the highest level of education were more likely to adhere to cervical cancer screening (96). The study proposed health literacy as a possible explanation for this, stating that people with lower levels of education have a lower capacity to obtain, process, and understand basic health information and services needed to make appropriate health decisions (96).

Besides, the review on the impact of level of education on adherence to breast and cervical cancer screening also acknowledged that this association could also be a result of individual level factors such as income, which is linked to level of education as well. Taking this into consideration in this review, it can be argued that women with lower levels of education are at a higher risk of cervical cancer mortality because they are less likely to adhere to screening services. Several mechanisms and factors that result from low education, such as low health literacy and income, pose limitations on their ability take advantage of available cancer screening and treatment services, thus resulting in inequalities mortality. The educational gradient in cervical cancer mortality observed between the low and medium education groups, when compared to those with high education supports this notion. An additional level of

education significantly alleviates the risk of adverse health outcomes an individual is susceptible to.

The prominence of the level of education as a risk factor for cervical cancer mortality, as well as a source of health inequality, is especially witnessed in this review. Most included studies were from HICs which are contexts that have prevailed in the presence of organised screening programmes. The impact of education on the risk of cervical cancer mortality can also be viewed in a retrospective sense, in addition to these prospective limitations and therefore adverse outcomes. Due to low education levels, and thus low health literacy, women may be unaware of the increased cervical cancer risk associated with sexual and reproductive factors such as early start of sexual relations, having multiple partners, or multiple pregnancies. Combined with lower adherence to cervical cancer screening, and lower access to treatment health services (in the case of late diagnosis), the risk of cervical cancer mortality among this group remains high. Future research may focus on understanding the other sociodemographic characteristics of women within these educational groups, to map a life course perspective that can possibly point towards the mechanisms through which education affects the risk of cervical cancer mortality.

The production of health inequalities from education is closely tied to the reproduction of inequality within education itself (97). While education is considered an important factor in social mobility and the improvement of people's life conditions, such as health, factors such as gender, class, and race can shape the disability for educational success and therefore provide justifications for inequality (97). For example, inequalities in educational attainment point towards racial and ethnic groups being at a disadvantage. As suggested by the Minorities' Diminished Returns (MDRs) theory, educational attainment shows a weaker protective effect for racial and ethnic minority groups compared to the majority (98). Inequalities in education therefore stand as a global phenomenon, that paves the way for the disadvantages and disparities faced within health systems and in health outcomes, respectively. Beyond educational attainment being (un)favourable towards specific sociodemographic groups, it has been found that even when women attain education, the influence of unfavourable gender socialisation, gender norms, and gender differences, confine them to the reality of being overrepresented in lower paying jobs (79).

When we consider the variations of the risk of cervical cancer mortality across regions, the link between education and health calls for a more holistic perspective. The Dahlgren-Whitehead model theory points towards the essence of the link between education and health existing within the broader context of the health system, with several interrelated factors. Simply put, the nature of the welfare state, such as health and education policy, present in a particular context, determines the intensity of the advantages or disadvantages in the association between education and health. This review revealed that the attainment of an additional level of education reduced the risk of cervical cancer mortality to a greater extent in the Nordic countries, compared to countries in Southern Europe. Considering the education system, Nordic countries offer free or low-cost education to all citizens regardless of their nationality. The nature of this public education system could entail that most individuals have access to the

same quality of education, regardless of their socioeconomic backgrounds. However, the same does not apply in Southern Europe, possibly implying that the quality of education attained by individuals in these regions can vary based on socioeconomic background and ability. This also has the potential to negatively affect the economic prospects an individual experiences, thus increasing cervical cancer risk. If we factor in gender, the reality that women are vulnerable to low pay, regardless of their qualification, makes exposure to lower quality of education a source of exacerbating that reality.

Besides, when we consider the healthcare system, Nordic countries have universal access to healthcare systems, which are mainly publicly financed through taxes with minor private health care sectors and limited private medical insurance (99). Due to this, those with low educational levels in the North stand at an advantage as they are more likely to access quality care, regardless of the economic constraints posed by low educational attainment and the economic pressures imposed by cervical cancer. This take on the link between education and health resonates with what Esping-Anderson argued for in '*The Three Worlds of Welfare Capitalism*', stating it is more beneficial to focus upon what a welfare state does (quality vs. quantity) (100). This argument brings forth the aspect of decommodification- the extent to which individuals and families can maintain a normal and socially acceptable standard of living regardless of their market performance (100). Of which, market performance can largely be determined by level of education. In addition to taking on this holistic perspective, further research can also consider trends in cervical cancer mortality within these regions, with reference to landmark education and health policy reform. This could identify enablers and disablers of efforts towards reducing cervical cancer mortality among vulnerable populations such as those with low education levels. This approach also acknowledges the findings in this review, that the influence of education on the risk of cervical cancer in the regions was not significantly different, despite varying effect sizes.

When we consider the age stratified analysis, the findings in this review support the hypothesis that the risk of cervical cancer mortality varies by age. The striking disparity of this risk, however, calls for the need to dwell on the impact and importance of education on younger age groups. Since studies have shown the inequalities in longevity according to level of education, it would be anticipated that older age groups would therefore have higher mortality compared to younger age groups (101). However, based on our results, it can be argued that the cumulated effect of the 'age at risk' of cervical cancer is observed. Cervical cancer is most frequently diagnosed in women between the ages of 35 and 44 with the average age at diagnosis being 50 (102). The interplay of high incidence among this cohort and the socioeconomic disadvantages posed by lower educational attainment may result in the higher mortality risk. Again, since low educational attainment inhibits adherence to screening, late diagnosis among this specific cohort increases the risk of mortality, a risk which could significantly be shadowed when the mean risk of mortality for a wider age cohort is considered, as seen in the results. Further research can explore cervical cancer survival, with age, education, and another key sociodemographic factor such as income. The variations can suggest how, for example, the (dis)advantaging effect of income on education and risk of cervical cancer mortality is less or more prominent for specific age cohorts, thus explaining our findings.

4.1 Limitations and strengths of the study

This review affirms consensus in health inequalities research that individuals with low level of education are at a greater risk of mortality. The effect of an additional level of education, and therefore importance of promoting education, has especially been observed when the regional analysis between Northern and Southern Europe was conducted. Besides, it has been found that younger cohorts are at a greater risk of cervical cancer mortality when we consider the influence of education. Therefore, they should be a key target group in the actions taken to address the inequity and inequality in cervical cancer mortality. While this review is a comprehensive synthesis of the influence of education on cervical cancer mortality, findings and interpretations ought to be taken with consideration due to the study's limitations.

4.1.1 Limitations

To begin with, the thesis has shortcomings in the geographical representation of included studies. Despite this being a global review of educational inequalities in cervical cancer mortality, there were no studies from LMICs. This was mainly a result of LMICs reporting 'all-cause mortality' effect sizes that included cervical cancer. Further, some studies in LMICs conducted survival analyses of cervical cancer, which did not fit our inclusion criteria's outcome of interest.

The adjustment of confounders is another limitation of this study. Of the 13 studies included in this review, only 4 adjusted for confounders. Controlling at a minimum when exploring education and inequalities might be preferred because some factors such as income are determined by education level, thus controlling might capture a part of the effect. However, not being able to adjust for some co-founders, particularly those that are not related to education such as age, may have resulted in an overestimation of the effect size of education. This, for example, was evidenced in the qualitative synthesis of this review. Not only did the study that controlled for the most co-founders suggest no association between the level of education and cervical cancer mortality, but one sub-group analysis further suggested that those with primary education were less likely to die from cervical cancer mortality compared to those with higher education.

The issue of quantity vs. quality of education is another limitation of this study. Firstly, while the transformation of educational categories into years of education using the ISCED mappings facilitated comparison, the aspect of quality of education, especially within the same level/specialisation, was not considered. The quality of the education achieved, beyond the years of education itself, may play an important role in the association with mortality. Secondly, the ISCED groupings did not allow for the differentiation of sub-groups within the main group. For example, the category, 'high education' which was ISCED 5 and above, did not distinguish between bachelor's, master's, etc. level, all of which may result in important variations in the association. Lastly, the years of education derived from the level of education were not equal for each country. As such, the "low" "medium" and "high" recategorizations did not have consistent years of education between studies. For example, in some studies the "medium" category constituted 10 to 13 years of education, while in others it was 9 to 11 years

of education. This may also play an important role in the variations of association between education level and cervical cancer mortality observed between studies, as well as in the education gradient of mortality reported in this review.

All in all, while comparison between studies was successful considering these limitations, clear pathways of association between level of education and cervical cancer mortality could not be explicitly concluded. This review outlined several theories about the influence of education on health outcomes. In our case, it cannot be stated if, for example, cervical cancer mortality due to lower educational attainment was a result of low financial resources or low health literacy (material factors vs. behavioural factors in the social causation theory).

The possibilities of misclassifications of educational level can also not be ruled out, as majority of the data was from population registries which include self-reported data on socioeconomic factors. Besides this, since most of the data came from population registries, they have the potential to exclude or have low representation of some social groups such as migrants, despite studies being representative of the entire population.

Finally, the age and region stratified analysis in this review had a limited number of studies. Thus, the generalisability of findings in the global context may not be justified, even for other European countries due to limited representation and overall limitations.

4.1.2 Strengths

The study applied a very rigorous methodology, along with justifications, for inclusion and exclusion, as well as consultations from universal standards of classifying/defining diseases and education to allow for comparison. Due to this and to our knowledge, this is the most comprehensive global review of educational attainment and cervical cancer mortality. Besides, the search string and review process did not have any language restrictions, thus allowing for a wider global pool of articles on the topic of interest to be identified and included. Regarding the meta-analysis, despite years of education not being equal in the education categories for each study, categories were still reflective of the ‘years of education’ range for the relevant ISCED level grouping. This allowed for the comparison of the association between level of education and cervical cancer mortality, including the change in gradient with every additional level of education. Besides, the variations in the association across regions was also observed, including the changes in gradient with every additional level of education, as well. Since this meta-analysis only included cohort studies, the risk of numerator-denominator bias and subsequent overestimation of the effect was eliminated. This is a well-known limitation to unlinked cross-sectional studies resulting from the non-comparability of educational information gathered from death certificates, and information gathered from the population census (103). Lastly, given the high heterogeneity in the analyses, the use of a random-effects model gave a much more robust effects model.

4.1.3 Implications and future research

This review offers empirical support for formulating and reforming policies that aim to improve health and well-being. It showcases the need to adopt efforts that address inequities in cervical cancer mortality, as those that are most vulnerable have been identified and can therefore be prioritized in such efforts. Besides, this review presents the need to not only increase access to education, but also promote advancement, due to the significant reductions in the risk of cervical cancer mortality through an additional level of education. The review also reveals the need to prioritize younger populations when promoting education, as they face increased risk of cervical cancer mortality. Finally, this review also presents the need to understand the underlying structures in which cervical cancer mortality inequalities, especially between regions, are produced and reproduced.

Although this review offers valuable empirical evidence, further synthesised research is needed on the topic of cervical cancer mortality and education. To begin with, more research is needed to understand the effect of age on educational inequalities in cervical cancer mortality. As proposed by the theory of intersectionality, for example, there are a multiplicity of factors at play within the link between education and health, such as age. Understanding its pathways of influence in this link would explain evidenced inequalities. This can be facilitated by incorporating a cervical cancer survival analysis approach. This would provide perspective on the socioeconomic characteristics of cervical cancer survivors and suggest the possible pathways in which education influences health and mortality, as well as the effect of age on educational inequalities in mortality. For example, the impact of income, which is determined by level of education, on survival for different age groups may be observed. Thus, the ‘material resource’ benefits of education, and their accumulation across the lifespan would explicitly explain educational inequalities in mortality, as well as the age disparities evidenced, even when considering the same level of education.

Future research can also consider the underlying structures that produce inequities within regions, and therefore result in geographical inequalities in cervical cancer mortality. This can range from an evaluation of health systems service provision in tandem with people’s access to care, to an evaluation of the education system and people’s access. Besides, the influence of gender ought to be considered in this case. An evaluation of gender policy can shed light on the limitations and opportunities women encounter based on their level of education within specific regions, and thus explain inequalities. On the same note, future research can also monitor the trends in the association between cervical cancer mortality and education level, with reference to landmark policy reforms in both the health and education sector. This would possibly help identify and uphold the strength of initiatives and interventions that have improved health outcomes from past to present, to promote health and well-being for all, and explain inequalities in cervical cancer mortality across regions.

Finally, where feasible in LMICs, future research can incorporate the use of longitudinal raw datasets to explore the influence of level of education on cervical cancer mortality. This would address the low geographical representation in LMICs, which largely reported all-cause

mortality outcomes. Further to this, the use of such datasets even in HICs would address the high levels of heterogeneity found in this review and allow for justified generalisability.

5.0 Conclusion

The influence of level of education on cervical cancer mortality is undisputed, with inequalities being the strongest when comparing low to high education groups. An additional increase in the level of education significantly decreases the risk of mortality. This gradient effect is especially observed when regional variations are taken into consideration. While the results suggest that differences in the risk of cervical cancer mortality are not statistically significant between the regions considered, it is important to consider the factors that have given rise to these contextual variations. This could include evaluating education, health, and gender policy, to understand the structures in which inequities are produced and inequalities are reproduced. When it comes to age, the influence of level of education on the risk of cervical cancer mortality is higher among younger cohorts. It can be argued that this is a result of the combination of the higher prevalence of cervical cancer among younger age groups (population most at risk), along with the socioeconomic disadvantages already faced by people with low educational attainment. The importance of education among younger age groups is strongly evidenced, and future research ought to explore the underlying mechanisms for the strong effect of age on educational inequalities in mortality. Overall, this review offers a basis for evidence-based policy that seeks to close both the inequity and inequality gap in cervical cancer mortality by revealing the most vulnerable population groups. Further research can expand on identifying the sociodemographic characteristics of those that are more likely to survive to explicitly suggest the pathways of education's influence on health. Besides, monitoring trends in cervical cancer mortality can facilitate identifying and upholding the strength of initiatives and interventions that have improved health outcomes when results are reflected upon in the wider context. It would continue to inform efforts tailored towards addressing health inequalities and inequities.

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Appendix

Appendix 1. Literature search string

ALL ((adult OR women OR men) W/10 (education OR educated OR "educational attainment" OR educational OR "educational attainment" OR "education level" OR "socio-economic status" OR socioeconomic OR "socioeconomic status" OR "social class" OR disparities OR differences OR income OR occupation OR "occupational position" OR "occupational inequalities" OR "social inequalities" OR "socioeconomic position" OR "health inequalities" OR "health equity" OR inequalities OR equity OR schooling OR literate OR literacy OR graduation OR "years of school" OR "school attendance" OR diploma OR "educational status" OR "social status" OR ethnicity OR employment OR gender OR emigrant* OR immigrant* OR poverty OR geography OR "marital status") W/10 ("cause specific mortality" OR "mortality rate" OR death OR mortality OR "total mortality")) AND PUBYEAR > 1979

Appendix 2. Critical appraisal

Table A1: Grading system for quality assessment of cohort studies

0-3	Fair
4-7	Good
8-11	Excellent

Table A2: Quality assessments of included studies

Author	Study design	Quality score	Quality level
Fernandez & Borrell (1999)	Retrospective cohort	10	Excellent
Jasilionis et al., (2015)	Retrospective cohort	10	Excellent
Smailyte et al., (2012)	Retrospective cohort	9	Excellent
Martínez et al., (2009)	Retrospective cohort	8	Excellent
Simon et al., (2012)	Retrospective cohort	7	Good
Li et al., (2012)	Retrospective cohort	10	Excellent
Menvielle et al., (2005)	Prospective cohort	8	Excellent
Singh & Jemal (2017)	Retrospective cohort	7	Good
Elstad et al., (2011)	Retrospective cohort	8	Excellent
Vries et al., (2015)	Retrospective cohort	7	Good
Simard et al., (2012)	Retrospective cohort	7	Good
Reques et al., (2014)	Prospective cohort	9	Excellent
Faggiano et al., (1995)	Retrospective cohort	11	Excellent

JBI Critical Appraisal Checklist for cohort studies

Reviewer _____

Date _____

Author _____ Year _____ Record Number _____
Yes No Unclear Not applicable

- | | | | | |
|---|--------------------------|--------------------------|--------------------------|--------------------------|
| 1. Were the two groups similar and recruited from the same population? | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 2. Were the exposures measured similarly to assign people to both exposed and unexposed groups? | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 3. Was the exposure measured in a valid and reliable way? | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 4. Were confounding factors identified? | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 5. Were strategies to deal with confounding factors stated? | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 6. Were the groups/participants free of the outcome at the start of the study (or at the moment of exposure)? | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 7. Were the outcomes measured in a valid and reliable way? | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 8. Was the follow up time reported and sufficient to be long enough for outcomes to occur? | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 9. Was follow up complete, and if not, were the reasons to loss to follow up described and explored? | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 10. Were strategies to address incomplete follow up utilized? | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 11. Was appropriate statistical analysis used? | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |

Overall appraisal: Include Exclude Seek further info

Comments (Including reason for exclusion)

