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Faculty of Health Science - Department of community medicine

Master's Thesis in Public Health

(Oral contraceptive use and risk of mortality among Norwegian women – a prospective study from the NOWAC study)

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Preface

It has been a great journey studying at UiT-The Arctic University of Norway. Collaborating with international students with diverse academic background allowed me to gain invaluable experience and knowledge. I have spent about a year in the public health sector in Nigeria as a public health officer, however, I felt the need to polish and enhance my skills where my teachers at UiT helped me greatly.

Working and researching drugs is something I have always had great interest in, and my supervisor Tonje Braaten was very helpful in expanding my knowledge in the aspect of oral contraceptives and to my co-supervisor Faith Benebo for helping a great deal with my statistical analysis.

Lastly, I'd like to thank Dr Femi Oyeyemi for providing me with a lot of insight on my thesis on what to research on and the necessary information to input.

I am thankful to my family for providing words of encouragement when things were looking so bleak.

Abstract

Background and theory: Millions of women are dependent on the use of oral contraceptives in order to have a more meaningful life and a general sense of well-being. Oral contraceptives enable women to control their reproductive life and manage other aspects of their life such as education, career, and family. These benefits make oral contraceptives one of the most prescribed medications among women. However, while there is established evidence on the short-term effects of oral contraceptive use, there are conflicting reports on the long-term risk of oral contraceptive use, especially regarding mortality. This study aims to explore the long-term association between oral contraceptive use and risk of mortality in a prospective cohort study of Norwegian women using the Cox proportional hazard model.

Methods: We gathered self-reported data from 126 786 women in the Norwegian Women and Cancer study's nationally representative cohort study. We obtained data on Oral contraceptive use, including duration of use and age at first use. Information on the outcome mortality was obtained from the Norwegian cause of death registry (which is regularly updated) during follow-up, in addition to covariate information. The association between Oral contraceptive use and the outcome mortality was assessed using Cox regression analysis. Respondents who had missing data on the exposure were excluded. Missing data on variables and participants lost to follow-up were excluded. Duration of Oral contraceptive use and age at first oral contraceptive use were assessed for trend and as categorical variables.

Results: Based on 11 310 deaths, we found no overall difference in mortality among women who had ever used oral contraceptives compared with women who had never used oral contraceptives. The hazard risk for ever-users, adjusted for age, was 0.95 (95% CI, 0.92 to 1.00). We observed a trend in no risk for total mortality with increasing duration of OC use of oral contraceptives. After adjusting for age, body mass index, cigarette smoking, education, physical activity, and the number of children, women who had used oral contraceptives still had no risk of mortality of 0.98 (CI, 0.95 to 1.02).

Conclusion

The use of Oral contraceptives is safe; no evidence from this study indicates that long durations of oral contraceptive use adversely affect long-term risk for mortality.

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Keywords and abbreviations

NOWAC – The Norwegian women and cancer study

OC- Oral Contraceptives

LARC- Long-acting reversible contraceptives

RCGP- Royal College of General Practitioners (RCGP)

CVD- Cardiovascular deaths

BMI- Body mass index

HR- Hazard ratio

CI- Confidence interval

SPSS- Statistical Package for Social Sciences

EPIC- The European Prospective Investigation into Cancer and nutrition (EPIC)

WHO- World Health Organization

1 Purpose of this thesis

The Norwegian Women and Cancer (NOWAC) study is a prospective cohort study that was initially developed to study the relationship between female cancer such as breast cancer and internal and external or artificially developed hormones. The study has self-reported information on women's oral contraceptive use, as well as information on mortality which was linked from the Norwegian cause of death registry and regularly updated. Oral contraceptives have been used in the US for 60 years and over 50 years in Norway, and while the short-term effects are well documented, there are ambiguous reports on the long-term use of oral contraceptives and mortality. Studies are indicating a protective factor of oral contraceptive use, while other studies indicate no association between oral contraceptive use and mortality. These findings led us to ask the research questions: *What is the strength of association between Oral contraceptive use and mortality in a cohort of Norwegian women? Is there a protective factor to long-term use of oral contraceptives, no risk of mortality, or increased risk of mortality with long-term use of oral contraceptives?*

The purpose of this study is to explore the long-term association between oral contraceptive use and risk of mortality in a prospective cohort study of Norwegian women using the Cox proportional hazard model.

2 Introduction

Oral contraception is a widely used and well-accepted method of contraception worldwide. Oral contraceptives have been available for over 40years and, although their short-term effects on health have been studied in detail (Royal College of general practitioners 1974, Vessey et al., 1976), comparatively little is known about whether these effects persist after use stops.
Unplanned pregnancies account for around 82 percent of pregnancies among women aged 15 to 19, and 60 percent of pregnancies among women aged 20 to 24 in developed countries (Darroch et al. 2001; Finter and Henshow 2006). Even though most women in these age groups use contraceptive methods, this high rate exists (Mosher et al. 2004). However, in underdeveloped countries, the above numbers are different from those in developed countries (Singh et al. 1998).

Oral contraceptive use has been advancing dramatically since its introduction in the 1960s, and an increasing number of people are using them. In 2015, the rates of married or in-union women aged 15 to 49 years who used oral contraceptives in the United States and the United Kingdom were roughly 16% and 28%, respectively (Benagiano 2006; UN 2015). Contraception is also commonly used in Western Europe, with an estimated 43.5 percent of reproductive-age women using it (UN 2005). According to a Swedish study, 65 to 88 percent of women currently use or are former users of OCs (Roswal et al. 2017; Ranstam et al. 1993; Kopp Kallner et al. 2015; Kumle et al. 2002), and the rate is rising. In Norway, about 21% of women under study used oral contraceptives as of 1994, while about 30% used other forms of contraception like IUDs (Skjeldestsad 1994). In a study by Furu et al., Combined oral contraceptives (COC) were still the most used hormonal contraceptive method in all age groups between the periods of 2006-2018 in Norway. However, this study also reports a decline in the use of COCs during the period, especially in those < 25 years, where a corresponding increase in the use of new and long-lasting forms of contraceptives such as long-acting reversible contraceptives (LARC) has taken place, mainly from 2014 onwards (Furu et al.,).

There is no doubt that humankind has benefitted in numerous ways through the innovative development of safe and effective contraceptive methods (Barot 2008; Cleland et al. 2006; Lule et al. 2007). Millions of women worldwide have been using oral contraceptives, and in

America, it is the most prescribed prescription for women aged 18 to 44 (Cogliano et al., 2005). The rate of pregnancies declines in more affluent societies (Speroff and Fritz 2005). This decrease is a result of the increased usage of contraceptive methods. Furthermore, the level of education and socioeconomic well-being of a person are crucial determinants in utilizing contraception (Singh et al. 1998). Surveys of the general population have revealed that the most significant demand for contraception is among adolescents and women over the age of 35, at either end of the reproductive range (Burkman Jr 1995). The relationship between reproductive rights and women's empowerment and the importance of contraceptive use is undeniable. In order to safeguard other aspects of women's and human rights, the ability of women to control their sexuality and fertility through appropriate contraception must be established first (Bongaarts 2014; Barroso 2010; Fantahun 2006). Oral contraception helps prevent pregnancy and can alleviate menstruation symptoms (Oinonen & Mazmanian, 2002).

Additionally, Oral Contraceptives have significantly decreased the personal and societal burden associated with unintended births, particularly the burden associated with maternal fatalities, to a remarkable degree (Maguire & Westhoff, 2011). A study claimed that if women of reproductive age did not utilize oral contraceptives, maternal deaths would be 1.8 times higher (Ahmed et al., 2005). There are numerous reported health benefits associated with contraception, including established benefits such as less functional ovarian cysts and new benefits such as a lower risk of colon cancer (Luan et al., 2015). Furthermore, oral contraceptives give women the ability to manage their reproductive health and, as a result, other parts of their lives, such as their careers and families (Charlton et al., 2014). Research has shown that a wide range of diseases, such as dysmenorrhea and fibroid-related symptoms, acne, and premenstrual dysphoric disorder, can be alleviated using oral contraceptive pills (Maguire & Westhoff, 2011).

Despite the advantages mentioned earlier, studies have highlighted concerns about the potential adverse effects of OC use, including the possibility of life-threatening negative consequences. For example, several studies have found that people who use OCs regularly are at an increased risk of ischemic stroke (Peragallo et al., 2013) and cervical cancer (Gierisch et al., 2013). Findings have also shown that the use of oral contraceptives (OC) that include both estrogen and progestin increase the risk of thrombosis, coronary heart disease (CHD), stroke, and breast cancer, while decreasing the risk of ovarian and uterine cancer (Rosendaal et al., 2003; Beral et

al., 1999; Dunn et al., 1999; Tanis eta al., 2001; Rosenberg et al., 2001; Gillum et al., 2000; Kumle et al., 2003).

With these advantages and disadvantages highlighted, it is also essential to clarify whether there are risks of mortality with OC use or not. There are several types of Hormonal Contraceptives, yet Far more women use combination OCs, and as a result, most epidemiologic studies consider this type, particularly the formulations popular during the 1960s to mid-1970s. Furthermore, it is for this reason that this study is focusing on Oral contraceptives.

3 Background and Theory

To adequately investigate the research question, background knowledge is needed regarding what oral contraceptives are, why oral contraceptives were developed, the economic and health benefits of oral contraceptives, prevalence of Oral contraceptive use as well as the association of Oral contraceptives to the outcome, mortality in our study. We researched what was known about this relationship, and what results were to be expected, as well as where theory might be lacking. In addition, we surveyed the relationship between women and the exposure and outcomes used in our study. Finally, we examined whether any of the reported covariates had a potentially confounding effect on the relationship between Oral contraceptive use and outcomes.

3.1 Oral contraceptives

Oral contraceptives also known as birth-control pills are medications taken by mouth to prevent pregnancy. The most common type of oral contraceptive pill is the combined hormonal pill with estrogen and progesterone. Estrogen and progesterone are two female sex hormones produced naturally in the body. Combination pills contain synthetic (man-made) forms of the estrogen and progesterone. The combinations of estrogen and progesterone work by preventing ovulation (the release of eggs from the ovaries), changing the lining of the uterus (womb) to prevent pregnancy from developing and changing the mucus at the cervix (opening of the uterus) to prevent sperm (male reproductive cells) from entering. Oral contraceptives do not prevent the spread of human immunodeficiency virus (HIV, the virus that causes acquired immunodeficiency syndrome [AIDS]) and other sexually transmitted diseases, however, are a very effective method of birth control if used correctly (Medline 2021).

Types of Oral contraceptives include Monophasic pills, Multiphasic pills and Extended cycle pills all of which differ in duration of use and hormonal levels. Investigating further leads us to why oral contraceptives were developed in the first place thus bringing us to the public health challenge of unintended pregnancies.

3.1.1 Unintended pregnancies

Unintended pregnancies are pregnancies that are mistimed (occurred earlier than wanted), unplanned or unwanted (did not want to be pregnant at all) at the time of conception. Unintended pregnancies include at least for one of couples not wanting the pregnancy. A current definition of unintended pregnancy also includes women who are ambivalent about their pregnancy (Piccinino 1995). It is among the most troubling public health problems and a major reproductive health issue including accidental pregnancy and defined as a pregnancy that was undesired for one or both partners (Finer et al.,). Approximately 210 million women become pregnant worldwide each year of which 87 million are unplanned and 41 million continue to birth. Reports by Sonfield et al., showed that the total number of unsafe abortions in 2008 was 21-22 million worldwide and there were 22 unsafe abortions per 1000 women aged 15-44 years. Furthermore, Sonfield reported that mortality due to unsafe abortion estimates 47000 maternal deaths (that is 13% of maternal mortality in 2008). Approximately fifty percent of pregnancies in the U.S are unintended and about 48% of reproductive-age American women (15–44) have experienced at least one unintended pregnancy (Sonfield et al. 2011, Amani et al., 2010). The economic burden of unintended pregnancies revealed that of the 2.0 million publicly funded births in the United States, 51% resulted from unintended pregnancies, accounting for $11.1 billion in costs-half of the total public expenditures on births. In seven of the states, the costs for births from unintended pregnancies exceeded a half billion dollars.

Among Norwegian women, there is still evidence to suggest the high numbers of unintended pregnancies despite the widespread availability of contraception. One of the indicators of unwanted pregnancies which is rate of abortion was found to be high in young women, with observed rates rising from 26.3 to 27.6 per 1000 women aged 15–24 years between 2001 and 2011. As reported by Henry et al., total economic costs from Unintended Pregnancies in Norwegian women aged 15–24 years were estimated to be 164 million Norwegian Kroner (NOK).

Apart from the economic costs of unintended pregnancies, the emotional and health burden of unintended pregnancies among women and their families is also worthy of attention. Pregnancy intent is an important determinant of both short- and long-term maternal and child health outcomes (Gipson et al., 2008). A study on pregnancy intention, specifically unwanted and ambivalent, unveiled that an unwanted or unintended pregnancy was an indicator of increased

risk for some poor birth and maternal outcomes and should be considered in interventions aimed at improving the health of mother and child (Mohllajee et al., 2007, Dehingia et al., 2020). Unintended pregnancy also contributes to increased risks of maternal depression and parenting stress (Bahk et al., 2015).

3.2 The economic and health benefits of oral contraception

The above pieces of evidence bolster the need for a form of contraception like oral contraceptives and below are highlighted the economic and health benefits of oral contraceptives and contraceptives in general.

- Educational attainment – It has been reported by (Edlund and Machado 2015) that young women's access to oral contraceptives has improved education rates by 10%. A working paper by Hock (2007) finds that more than 250,000 women over age 30 were able to obtain bachelor's degrees as a result of contraception use hence decreasing dropout rates by 35%.
- Career – Studies by Goldin and Katz 2002 and Steingrimsdottir 2016 have disclosed that women are making up higher proportions of individuals with careers in professional fields. Among college-educated women, access to the contraceptive pill can be attributed to some of this increase.
- Poverty – As reported by Browne and LaLumia (2014) access to the contraceptive pill by age 20 reduces the probability that a woman is in poverty by one percentage point to 12.2 percent. In addition, it unveiled that contraceptive access impacts women's expectations for themselves and sense of empowerment more broadly, which may contribute to a reduction in poverty.
- Earnings – Early legal access to oral contraception improved women's wages more rapidly than women without access to the pill, resulting in substantially higher earnings by their 30s and 40s (Bailey et al., 2013).
- Workforce market – Access to oral contraceptive pills contributed to delayed motherhood and a 14-15% increase in the participation rates of women in the workforce and the number of hours worked by women (Bailey 2006).
- Impacts on the next generation - Due to the legalization of contraceptives, many women have been able to delay childbearing to get an education and earn more, thus reducing the number of children born into poverty (Bailey, Malkova, and Norling 2014). As birth

are retimed with oral contraceptive use, children are born to households where pregnancy is well intended, and child arrival is well prepared for. Also, the economic effects of contraceptive use have extended from childhood to adulthood with a substantial reduction in the number of adults living in poverty (Bailey, Malkova, McLaren 2018). Bailey 2013 also reported that children born to mothers with access to oral contraceptives were more like to complete higher levels of education. Research from Indonesia by Utomo et al., there has been a substantial decrease in the risk of maternal mortality which can be attributed to use of contraception.

These economic and health benefits of oral contraception are proof of how important oral contraceptive use is for women. Therefore, we would further delve into studies that either prove there is a risk or there is no risk of mortality due to Oral contraceptives.

3.3 Risk of Morbidity due to Oral contraceptive use

A study by Busund et al., has reported an association of Oral contraceptive use and an increased risk of breast cancer in the NOWAC (Norwegian women and cancer) Cohort study. More research on Oral contraceptive use has also revealed a raised risk of suicide behavior through the impact of sex hormones on mood (Marrocco & McEwen, 2016; McEwen & Milner, 2017). While some studies have found an increase in depression symptoms among women who take combination tablets (Gregory et al., 2018; Kulkarni, 2007; Skovlund et al., 2016), others have found a negative association or reported null findings (Keyes et al., 2013; Toffol et al., 2011, 2012; Worly, Gur, & Schaffir, 2018; Zethraeus et al., 2017). The impact of sex hormones on mood and behavior is well documented (McEwen & Milner, 2017), and some prior research has found a positive link between OC usage and depressed symptoms (Skovlund, Morch, Kessing, & Lidegaard, 2016), albeit the findings are inconsistent (Keyes et al., 2013). The findings of a study conducted by Skovlund et al. (2018) utilizing Danish registry-based data and a sample size of nearly half a million women revealed a positive connection between contraceptive use and the likelihood of suicide behavior (attempts or completions) among women. The analysis revealed that the probability of a first suicide attempt was highest in the first two months of contraceptive use and remained raised for at least one year following the start of use; women aged 15–19 were at greater risk than women aged 20 or older. According to the findings of their study, the probability of having a suicidal event increased after starting contraceptive use. With regards to stroke, it remains a debatable issue in the existing literature

whether women taking OCPs are at an increased risk of stroke (Petitti et al. 1996; Schwartz et al. 1997; Nightingale and Farmer 2004; Yang et al. 2009; Gallagher et al. 2011). It is observed in a meta-analysis that females who currently take OCPs have a higher risk of first-ever ischemic stroke (IS) (Xu et al., 2015). Similar results in another meta-analysis showed that current OCP use led to a slight increase in hemorrhagic stroke (HS) incidence (Xu et al., 2018).

3.4 Risk of Mortality due to Oral Contraceptive use

A large number of studies conducted in developed countries (especially in the United Kingdom and the United States) found that there is a positive correlation between oral contraceptive (OC) use and risk of mortality from various circulatory system diseases, for instance; pulmonary embolism, cerebral thrombosis, and myocardial infarction (Beral 1976; Beral & Kay 1977; Bickerstaff ER, &Holmes 1967; Illis et al. 1965; Inman &Vessey 1968; Mann & Inman 1975; Mann, & Vessey 1975; Oliver 1970; Radford & Oliver 1973; Sartwell 1969; Stolley et al.1975; Vessey & Doll 1975; Zilkha 1965). In addition, various research has been conducted in many other countries to explore whether the increased prevalence of oral contraceptive use among women of reproductive age increased mortality from circulatory system diseases (Beral 1976; Belsey et al. 1979; Tietze 1979). However, whether these findings are applicable in the developing countries context remains a matter of concern for health and family planning administrators (Belsey et al., 1979; Tietze, 1979).

Although there is a concern about this possibility, there are no established reports of a possible link between OC usage and an increased risk of death. All-cause mortality is not associated with the use of OCs in most studies (Charlton et al. 2014; Lu et al. 2011; Phillips, Trivers, and Graff-Iversen 2007; Graff-Iversen et al. 2006), but some studies (Hannaford et al. 2010) have found that OC users have a slight advantage in terms of all-cause mortality.

3.4.1 Mortality research showing no protective factor and no risk of mortality

The Oral Contraception Study conducted by the Royal College of General Practitioners (RCGP) featured 1,400 family doctors from around the United Kingdom who recruited approximately 23,000 women who were already using oral contraceptives and another 23,000 women who had never used one. They aimed to describe the long-term effects of oral contraceptives on mortality followed by a cohort study with 25 years of follow-up. Findings

showed a similarity in ever users and never users of oral contraceptives; that is there was no association between oral contraceptive use and risk of mortality though it was statistically non-significant when comparing ever users (present and former users combined) to never users the study (Royal College of general practitioners 1999). Nevertheless, there was a difference between current and recent users of oral contraceptives and women who stopped using contraceptives. Reports showed the relative risk of death from ovarian cancer was lesser, and the risk of mortality with cervical cancer and cerebrovascular disease among current and recent (within ten years) users was increased.

Another study by Graff-Iversen et al. (2006) examines the relationship between total and cardiovascular disease (CVD) mortality and the use of oral contraceptives (OC) in a cohort of women who had a disproportionately high prevalence of smoking and elevated serum cholesterol levels. From 1985 to 1988, the researchers invited a total of 29,053 women between the ages of 20 to 49 years old to participate in a health survey. They discovered 518 deaths, with ten of them occurring among the women using OC at the study's inception. In the study, two of the three CVD deaths among OC users occurred during the first year of follow-up. Three women died during the study's follow-up among non-smokers who used OC; cardiovascular disease was not the cause of any fatalities. The conclusion was that results were consistent with previous evidence which does not indicate that mortality from all causes or CVD is elevated in women using OC.

Nur et al. (2019) investigated the long-term impact of OC use on overall and cancer-specific mortality in Swedish women. Among 2120 women with breast cancer, 1268 admitted to using OC at some point in their lives, and 254 died within ten years of being diagnosed. All-cause mortality showed no association with mortality for OC ever-users, and there was also no association with breast cancer-specific mortality for OC ever-users compared to never-users. Moreover, according to their findings, among women with primary breast cancer, OC ever-users were not associated with a higher overall or breast cancer-specific mortality when compared to never-users.

In a study by Vessey et al., 1989, the objective of the study was to see whether the use of oral contraceptives influences mortality. A cohort study of 17,032 women were followed up on an annual basis for an average of nearly 16 years. During the period of recruitment each woman was aged 25-39, married, a white British subject, willing to participate, and either a current user

of oral contraceptives or a current user of a diaphragm or intrauterine device (without previous exposure to the pill). A total of 238 deaths occurred during the follow up period. From the findings of this analysis, there was no significant evidence of any overall effect of oral contraceptive use on mortality.

Another study conducted by Vessey et al. (2003) among 17 032 women aged 25–39 years explored mortality concerning oral contraceptive use and smoking. Based on the 889 deaths analyzed, they found that women who had ever used oral contraceptives had increased the mortality from cervical cancer and decreased mortality from other uterine and ovarian cancers. Furthermore, for women who smoke 15 or more cigarettes per day, it is found that oral contraceptives increase the risk of death from ischemic heart disease. Finally, their study concluded that on overall mortality, there was no harmful effect. However, death from all causes was more than twice as high in smokers of 15 or more cigarettes a day as in non-smokers.

Colditz GA (1994) conducted his study to investigate the mortality risk for women who had ever used oral contraceptives compared to women who had never used oral contraceptives. Between 1976 and 1988, Colditz conducted a prospective cohort study in which 166 755 women between 30 and 55 years old took part. With the number of fatalities (2879), findings demonstrate that there was overall no difference in mortality between women who had ever used oral contraceptives and women who had never used oral contraceptives. Therefore, based on this study, Colditz concludes that; the use of oral contraceptives is safe; no evidence from this study indicates that long periods of oral contraceptive use are associated with an increased risk of long-term mortality.

Using the Nurse health study: a prospective cohort study, Charlton et al. (2014) aimed to explore whether the use of oral contraceptives is associated with all-cause and cause-specific mortality. They followed 121701 participants for 36 years. Their results found no association between ever use of oral contraceptives and all-cause mortality. However, violent or accidental deaths were more likely among the former and current user when compared to never-users. Moreover, a longer usage duration was more strongly connected with some causes of death, such as premature mortality from breast cancer and lower mortality rates from ovarian cancer. Observation showed a connection between specific outcomes and a more extended period since the last usage, including a favorable connection with violent or accidental deaths.

3.4.2 Mortality research showing a protective factor from mortality

When comparing ever users of OCs to never users, the following studies found a statistically significant reduction in the probability of all-cause death (Vessey 2010; Hannaford et al., 2010, Britt & Short 2012). Data from the Oxford/Family Planning Association trial revealed there was a statistically significant difference in all-cause mortality between users of OCs at the time of study admission and users of the diaphragm or intrauterine device over a twenty-year follow-up period. (Vessey et al., 2010). However, the researchers stated they cannot be sure that this represents a beneficial effect of OCs, but the fact that the Rate Ratios decline with duration of OC use supports this view. In this analysis, the small number of categories of deaths that occurred limits the study's ability to detect substantial differences in risk between contraceptive groups. There was evidence of a slightly increased risk of cardiovascular death among pill users, primarily due to more myocardial infractions, despite that none of the cause-specific comparisons were statistically significant (Vessey et al., 2010).

Hannaford et al. (2010) used a prospective cohort study that started in 1968 with the mortality data supplied by participating general practitioners. They wanted to observe whether mortality risk among women who have used oral contraceptives differs from that of never users. In that study, around 378006-woman years of observation among never users of oral contraception and 819175-woman years among ever users participated, and they observed for up to 39 years. Results show that among never users of oral contraception, 1747 deaths occurred compared to 2864 death in ever-users. In addition, ever-users of oral contraception had a significantly lower death rate from any cause than never users

Furthermore, they claim that there was no correlation between overall mortality and the length of oral contraceptive use, while some disease-specific relationships exist. There was a significant increase in the relative risk of death from any cause between ever users and never users in women aged below 45 years who had stopped using oral contraceptives 5-9 years ago, but not in those who had stopped using oral contraceptives in distant past. The findings conclude that oral contraception was not associated with an increased long-term risk of death in the large UK cohort. There was a net benefit from using oral contraception.

Since oral contraceptive use can affect various health outcomes through different mechanisms, mortality provides a uniquely relevant estimate by combining different causes of death.

It is therefore important, that information be gathered through more epidemiological studies of human population (in this instance, the NOWAC study), in order that abnormal patterns of death among women using oral contraceptives maybe recognized as soon as possible and appropriate corrective measures instituted (Inman et al., 1968, Vessy et al., 1968).
In view of the range of effects of oral contraceptives we considered that the overall risk of mortality in the group of women involved in the NOWAC study would be of the greatest interest and contribute further to existing knowledge on oral contraceptives on whether oral contraceptive use poses a risk or not.

After reviewing the health risks of pregnancy and the benefits and risks of OCs, it is pertinent that we observe closely that the hazards of using oral contraceptives is not higher than the hazards of an unintended pregnancy.

3.5 Covariates

Unrecognized confounding factors are a significant analytic concern that can lead to erroneous conclusions (S. Greenland & Morgenstern, 2001) However, if these covariates are identified, they may help to "explain away" spurious associations and make possible the detection of significant relationships. The following are covariates as reported by respondents in the study. Possible association with Oral contraceptives and the outcomes we were looking for is examined in further detail below.

3.5.1 Age

From a Canadian study researching the use of oral contraceptives in association with age as a sociodemographic factor, an inverse relationship was observed with OC use decreasing with increase in age (Rotermann et al., 2015). Another study by Daniels and Abma 2018 supports this evidence where a study on current use of oral contraceptives unveiled that OC use was highest among women between age 20 -29 and was lowest among women aged 40-49.
Atramont et al.,2019 that studied the association of age with short-term and long-term mortality among patients discharged from intensive care units in France revealed that aging was associated with an increased risk of mortality among elderly patients in the 3 years after hospital ICU discharge, while excess long-term mortality was highest in young surviving patients, hence concluding that increase in age increases risk of mortality. In a systematic review and meta-

analysis by Biswas et al., 2021 studying the association of sex, age, and comorbidities with mortality in COVID-19 patients, it was found that patients with age ≥50 years confirmed with SARS-CoV-2 infection were associated with 15.4-folds significantly increased risk of mortality as compared to patients with age <50 years. These provide the basis for using age as a covariate (and adjust for it) to ensure it is not acting as a confounder in this analysis.

3.5.2 Body mass index

Increasing body mass index (BMI) is also recognized as a risk factor mortality as seen with aging. In a global status report on noncommunicable diseases by (Alwan 2010) WHO states that: "Mortality rates increase with increasing degrees of overweight, as measured by BMI. To achieve optimal health, the median BMI for adult populations should be in the range of 21 to 23 kg/m2, while the goal for individuals should be to maintain a BMI in the range 18.5 to 24.9 kg/m2, and moderate to severe risk of co-morbidities for a BMI less than 30 kg/m2.

In a 2011 study by the Norwegian institute of public health, 1 in 5 Norwegians were reported to be obese. There was no significant difference between genders, except for a female dominance in the older age groups (Helsedirektorat 2011). Heather et al in 2010 published reports on risk factors for mortality in the Nurses' Health Study which also indicated increasing risk of mortality with increased BMI. On the other hand, based on the association between BMI and Oral contraceptive use, a 2016 data analysis of among Ethiopian adult women of reproductive age revealed that there is a significant association with oral contraceptive use and BMI. The analysis showed that use of combined OC increases the odds of overweight/obesity by two times among adult women of reproductive age after controlling for potential confounders. However, when Mayeda et al., 2014 reported the weight and body composition changes during oral contraceptive use among obese and normal weight women, the findings revealed that OCs are not associated with short term weight or body composition change for normal weight women and suggest that OCs are also are not associated with short term weight or body composition change in obese women. In line with this, BMI was still included to ensure it still was not a confounder in this analysis.

3.5.3 Education

Education is a social determinant of health, both in form of what knowledge an individual has

access to and the possibility of understanding and applying it, but more importantly by the way it gives access to occupation and salary, and the lifestyle associated with these. As a social determinant of health, a lack of education has proven to be a risk factor for mortality and morbidity (Alwan 2010).

In a CDC report by Daniels et al., 2018 current pill use increased with higher education—4.9% of women without a high school diploma or GED were using the pill compared with 16.3% of women with a bachelor's degree or higher. Another study which supports the association between education and contraceptives by Tanfer and Horn 1985 stated that better educated women are much more likely than less-educated women to practice contraception, and women who work outside of the home are more likely than those who do not use contraceptives. In terms of mortality, people who have access to education are more likely to live longer and healthier lives. Not only does education provide the opportunity for an upward mobility but also for better financial circumstances (Blakely and Tobias 2008, Mackenbach 2003). Lesser years of education or none at all is linked to lower income, which is linked to poorer health. Numerous studies show that people in lower socioeconomic situations experience more obesity, asthma, diabetes, heart disease and ultimately death than people in better financial circumstances (Halpern et al., 2020, Hummer and Hernandez 2013, Wamala et al., 2006). In Norway, this trend is also visible with increased mortality associated with lower levels of education (Strand et al., 2010, Fawcett et al., 2005).

3.5.4 Alcohol consumption

Alcohol overuse is considered one of the major risk factors for non-communicable diseases such as cardiovascular disease which has also been linked to oral contraceptive use by several studies (Roach et al., 2015, Gillum et al., 2000). In a large European cohort by Ferrari et al., 2014 using the EPIC study, alcohol use was positively associated with overall mortality, violent death and injuries, but marginally to CVD/CHD. Absolute risks of death observed in EPIC suggest that alcohol is an important determinant of total mortality. Alcohol use has also been described by WHO as a causal factor in this same regard. In addition, there are studies showing an association between Alcohol consumption and oral contraceptive use, where using both has shown to increase lipid levels and lipoproteins in the blood (Kruszon-Moran et al.,1988). And

increased blood lipid levels have been indicated as a risk factor for cardiovascular disease Steinberg 2005)

3.5.5 Cigarette smoking status

Cigarette smoking has been indicated as a risk factor for diseases like lung cancer, cardiovascular disease and other types of diseases (Allen et al., 2019, Teo et al., 2006). Worldwide, there are about 1.3 billion smokers, most of which live in developing countries (Teo et al., 2006). Smoking as a social determinant of health also displays variation in prevalence within population subgroups. Lower socioeconomic groups have a higher prevalence of smoking (Kaczynsky et al., 2008). The world health organization has also reported that higher levels of daily smoking was found to be associated with lower levels of educations (Alwan 2010).

Lidegaard in 1999 studied the association between smoking, oral contraceptives and thromboembolic disease. The author concluded that the combination of smoking with oral contraceptive use may have a synergistic effect on risks of acute myocardial infarction and cerebral thromboembolic attack (but not of venous thromboembolism), particularly among users of high dose of OC

Also in 2010, Vessey et al., published reports on the factors affecting mortality with special reference to OC use. It was concluded that the overall mortality ratio for all women smoking 15+ cigarettes daily was 2.25 times higher compared to a non-smoker

3.5.6 Physical activity

Physical activity promotes health and longevity (Bauman et al., 2004, Kartzmarzyk et al., 2003) and increasing participation in regular exercise has been a major public health goal. The Centers for Disease Control and Prevention (CDC), and the American College of Sports Medicine (ACSM) recommend a minimum of 30 minutes of moderate activity on most days of the week (US department of health 1996). When Leitzmann et al., studied Physical activity recommendations and risk of mortality, they reported that following physical activity guidelines is associated with 27 % lower risk of mortality. A 32 % mortality benefit could also be achieved by engaging in less than recommended activity levels. This is also supported by Mok et al.,

2019 who reported that middle aged and older adults, including those with cardiovascular disease and cancer, can gain substantial longevity benefits by becoming more physically active, irrespective of past physical activity levels and established risk factors. And also, that considerable population health impacts can be attained with consistent engagement in physical activity during mid to late life. Zhao et al., 2020 have also reported that adults who engage in leisure time aerobic and muscle strengthening activities at levels recommended by the 2018 physical activity guidelines for Americans show greatly reduced risk of all cause and cause specific mortality. In relation to Oral contraceptive use and Physical activity, Merians et al 1985 studied change in blood lipid level among exercising and exercising women who were OC users or non-users. They concluded that blood lipid level decreased among progestin using exercising women

3.5.7 Number of children

As earlier discussed, unintended pregnancies are the leading reasons for why many women opt for oral contraceptive use. Unintended pregnancies have deprived women of an education, presence in the labor force and the increased psychological problems of an abortion. Women are also at a high risk of maternal mortality especially in developing countries. The World Health Organization estimates that more than 300,000 women died from pregnancy-related causes in 2015. That's 830 women every day (Our world in data, 2021). This begs the need for oral contraceptive use especially when the pregnancy is unintended. Therefore, increased number of children increases the need for oral contraceptive use (Gaddalla et al., 1985)

A study in Bangladesh has unveiled that woman whose husbands wanted fewer children had higher contraceptive use compared to when both wanted the same number or when the husband wanted more children (Hossein et al., 2018)

4 Materials and methods

This a study drawing data from the NOWAC study which is a representative national prospective cohort study that started in 1991. We used data collected in this study to examine the association between long-term oral contraceptive use and mortality. Information regarding the NOWAC study and its participants was obtained from the NOWAC study homepage on the internet, as well as articles describing the cohort (Lund et al., 2008 http://site.uit.no/nowac/.)

4.1 The Norwegian Women and Cancer (NOWAC) Study

The primary purpose of NOWAC was to create a large prospective cohort designed to study the relationship between internal and external hormones and female cancers with a focus on breast cancer. The University of Tromsø–The Arctic University of Norway initiated this study. All women were sampled randomly from the Norwegian Central Person Register, which contains information on all Norwegian inhabitants, including a unique identification number consisting of the date of birth and five other numbers giving a unique combination (Lund et al., 1980). This personal number is used in all linkages to give a complete follow-up through the national registers.

4.1.1 Questionnaires in the Norwegian Women and Cancer study

At the present time there exists one baseline and three follow-up rounds of questionnaires. Each round was separated by 4-8 years of follow-up time. The women were mailed an invitation with a photo booklet of all OCs or hormonal replacement therapy brands and a questionnaire. The questionnaire was used to collect information on oral contraceptive use including Status of oral contraceptive use, duration of use, status (dead or alive) collected from population registry, Hormone Replacement Therapy, age at entry, age at the start of periods, menopausal age, age of OC start, smoking habits, alcohol, and other relevant variables such as weight, height, dietary habits, family history of breast cancer.

4.1.2 Follow-up in the Norwegian Women and Cancer study

During the years 1991–97 altogether 179 387 women were invited, of whom 102 540 women (57%) aged 30–70 years returned a questionnaire to the Institute of Community Medicine, University of Tromsø, Norway. In 1998–2002, all women received an invitation to fill in a

second questionnaire, and 80 693 women replied (response rate 81% corrected for death and emigration).

During 2003–06 another 130 577 women born 1943–57 were invited, of whom 63 232 (48.4%) returned an eight-page questionnaire. Figure below displays the different series of questionnaires and the rounds of follow-up to which they belong, as well as the years in which these series were administered

The original researchers received approval from The Regional Committee for Medical Research Ethics to collect and store questionnaire information, blood samples, and tumor tissue from the present. All women filled in informed consent for later linkages to the register of death certificates in Statistics Norway. All data were stored and handled according to the permission given by the Norwegian Data Inspectorate.

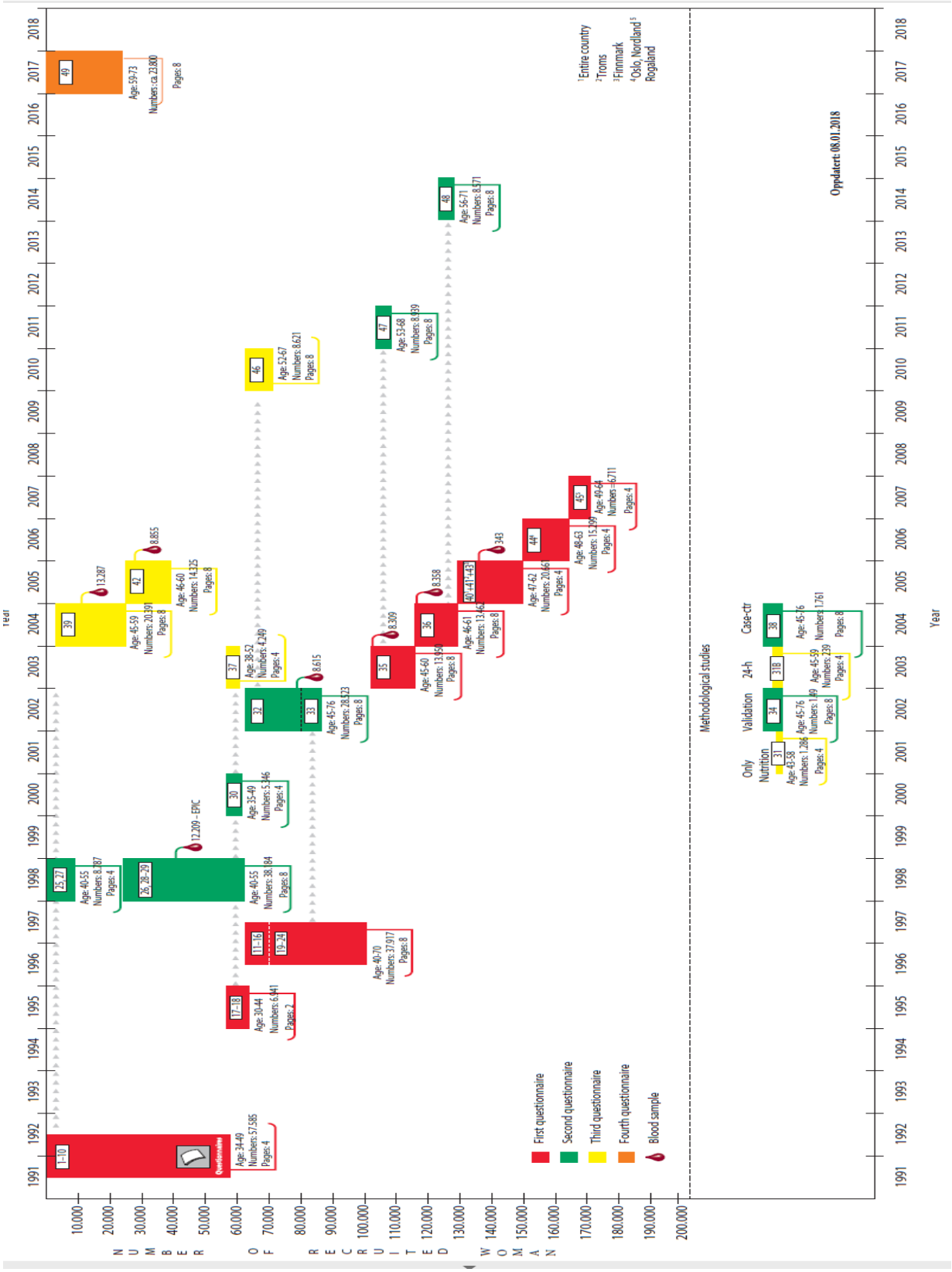

Figure 4.1 Cohort enrolment in the NOWAC study: participants, questionnaires, and baseline/follow-ups

4.2 Study population

We used information from the first questionnaire for the women enrolled in 1996 and later. For the women enrolled in 1991, we used information from both the first and second questionnaire, starting follow-up in 1998 to ensure that most of the women had ceased their use of oral contraceptives at study baseline.

The total number of included participants in the initial study population was 161 876. A total of 6794 participants did not have the OC use status; hence, we excluded them from the analysis. In addition, we excluded 33 respondents who emigrated or died before start of follow up, and participants who had missing information on important variables such as smoking status, Body mass index, alcohol drinking and education. Hence the total number of included participants in our final cohort sample were N=126 786. Figure 4.2 below displays the flow of participants eligible for our study produced by those series that contained relevant data on exposure and outcome.

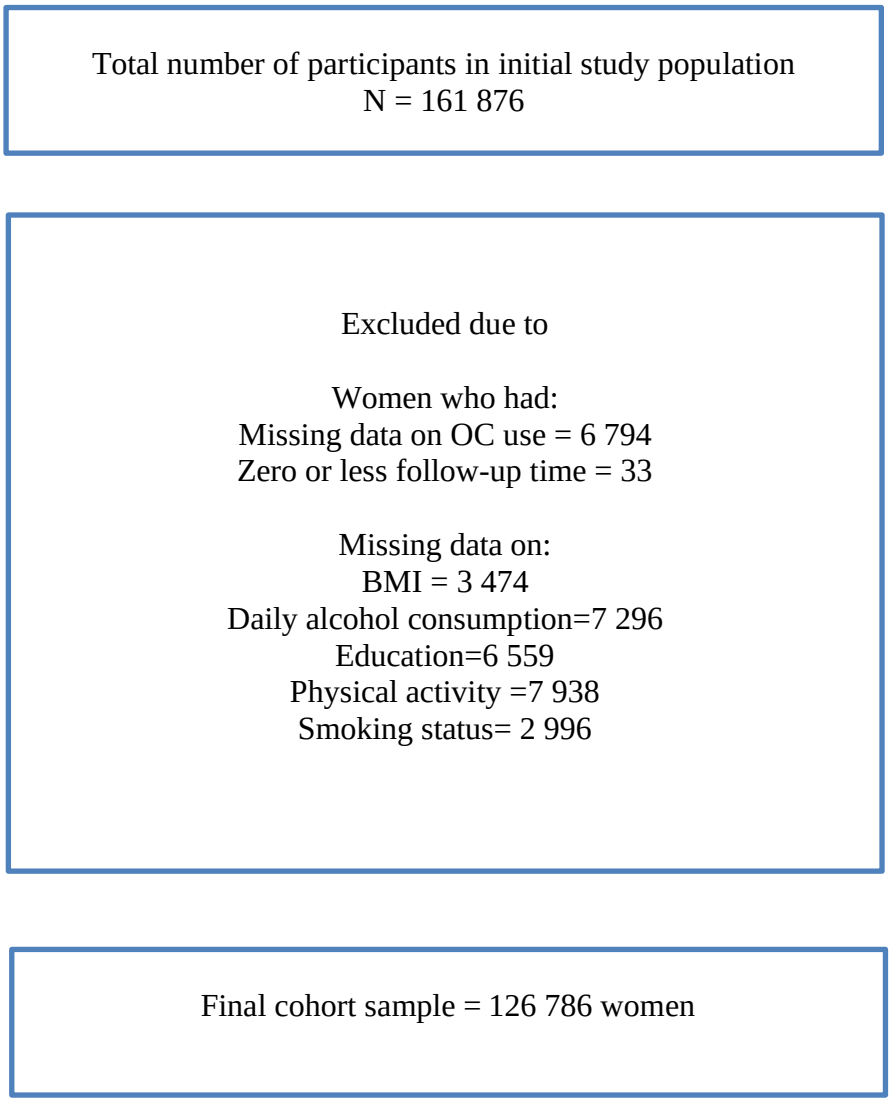

Figure 4.2 - Flowchart representing the exclusion criteria for the selection of final cohort sample.

4.3 Analysis of data

The following outlines how variables were gathered and coded from the NOWAC study and what statistical methods were used to assess the information.

4.3.1 Exposure and outcomes in the material

In this study, Oral contraceptive use was determined by self-reporting in a questionnaire. See appendix A for an example questionnaire from the NOWAC study.

4.3.1.1 Oral contraceptive use

The exposure variable for Oral contraceptive use was obtained from a nominal scale included in the original questionnaires. Participants were asked to "*Have you at any point used the pill or minipill after 1991"* with participants selecting "*yes or no*". Further questions were, "*If yes, how many years have you used the same contraceptive pill continuously? How old were you the first time you used the pill or mini pill?* Oral contraceptive use existed in the data set as a binary variable and was recoded into a two-category variable in preparation for analysis. Participants that selected *"no"* to OC use were coded as *"0=never-user",* while participants that had at any point used oral contraceptives were coded as *"1=ever users".* Category *"never-users"* was used as reference group in the cox regression analysis. Number of years of Oral contraceptive use was also determined by recoding ever users of Oral contraceptives into "<1-4 years", "5-9years", and "≥10". This manner of recoding Oral contraceptive use has previously been demonstrated on the same dataset and appears to be a functional manner of preparing the variable for cox regression analysis (Busund et.al). Age at first oral contraceptive use was another exposure variable recoded in "<20 years" "20-24 years", "25-29 years", and "≥30 years". Never users of OC were considered the reference group because they have not been exposed to oral contraceptive use, hence would not indicate any protective or risk factor. To facilitate recall, the questionnaires contained a photo booklet with pictures and names of the different OC brands available on the Norwegian market up to the time of mailing. As of 2015, no more than 42 different OC brands have been sold in Norway. The internal validity with regard to OC use assessment in NOWAC has been found to be satisfying (Lund et al., 2008).

4.3.1.2 Outcome measures

Information on participants who had died during follow up were all obtained from the Norwegian death registry and are well-updated each year. Participants are regularly tracked with the 11-digit Norwegian personal number which is linked to the Norwegian death registry. Participants gave informed consent on use of information from the death registry. The number of deaths used in this analysis are accurate as of the study year 2019.

4.3.2 Confounders

Confounders in this study as previously discussed were deemed of importance to the outcomes at hand and included in statistical modeling to assess their confounding effect on the association between Oral contraceptive use and the outcomes:

Age at enrolment was derived from respondents' year of birth. Age was used in the analysis as a continuous variable.

BMI at enrolment was calculated from participants' specification of current height and weight. BMI was recoded into the following categories in: "normal weight (BMI = 20-24.)"; "underweight (BMI < 20)"; "overweight (BMI = 25-29)" and "obese (BMI ≥30)". The category for normal weight was used as reference category in Cox regression analysis.

Duration of education was obtained by asking participants about their total length of education or vocational training. Education was grouped as following: "0-9 years", "10-12 years" "13-16" and "≥ 17 years". Category 1 was used as reference category in Cox regression analysis.

Alcohol consumption was recorded by asking participants whether they were completely abstinent, or if not, then how often they consumed one unit of beer (½ liter), wine (1 glass) or spirits (drinks), on average during the last year. Options included "never/seldom", "1 per month", "2-3 per month", "1 per week", "2-4 per week", "5-6 per week" and "1+ per day". Consumption was then calculated into grams per day. The data was recoded into four groups: "0.1-4.0 grams per day", "never user", "4.1-9.9 grams per day" and "≥ 10 grams per day". Category "never user" was used as reference category in Cox regression analysis.

Information on Smoking was obtained by asking if they were current smokers. This study used the variable displaying current smoking status, coded as "never", "former" and "current". Category "never" was used as reference category in Cox regression analysis. Form the first 10 series of questionnaires in the NOWAC study, the questions did not ask about current smoking habits but was derived from respondents reporting how many cigarettes they were currently smoking per day.

Number of children was obtained by asking participants *"Have you at any point been pregnant. If yes, fill out for each child you have given birth information about the year of birth and the number of months you breastfed (also fill in for stillbirths or for children who have died later in life). If you have not given birth, continue with the next question".* Respondents without information on number of children were classified as "none" and was used as reference category in Cox regression. Respondents with information on number of children were recoded into the following categories "1-2", "3-4" and "≥5".

4.3.3 Statistical methods

The following outlines the statistical methods used to assess the data gathered from the NOWAC study. This included both the descriptive statistics used to gain an overview of the distribution of variables within the selection, and the Cox regression analysis used to assess the association between exposure and outcomes.

4.3.3.1 Descriptive statistics

Descriptive statistics were used to obtain information on the study participants. Means and standard deviations were used to assess the dispersion of data, or median and percentiles if data were asymmetrically spread or prone to outliers. Visual binning was used to categorize variables into an appropriate number of bins based on pre-specified cut-off values or a pre-specified number of bins. Variables were grouped according to never-users or ever- users, to more easily compare the groups.

4.3.3.2 Cox regression models

Statistical analysis was performed using IBM Statistical Package for Social Sciences-SPSS V. 28. Cox proportional hazard regression was selected as the main method of analyzing the strength of association due to the dichotomous nature of the outcomes of interest and the prospective design of the study (Jekel et.al 2014). This would also allow controlling for possible confounders. A Cox regression model was made for the outcome mortality as the dependent variable. Hazard ratios (HRs) and 95% confidence intervals (CIs) were reported.

Univariate analysis of covariates against the outcome was performed preliminary. This was done to assess the predictive power of the covariates for the outcome. Significant variables were then included one by one in building a model for the outcome. Insignificant variables were finally added to the model to check for new significance levels. When building the final model, covariates that had a confounding effect of a certain magnitude on the main estimate of association were included. The level of confounding deemed necessary for a covariate to be included was set at <5%. Confounding was determined by comparing age-adjusted HRs for Oral contraceptives to HRs for Oral contraceptives when including each of the covariates separately. If HRs changed by 5% or more for any of the level of duration of OC use associations with the outcomes, the covariate was considered to have a confounding effect on the association between OC use and the outcomes and was subsequently included in the final model. In cases of doubt, when several levels lay close to but below the 5% level, we chose to include the covariate on basis of previously described theoretical knowledge that a relationship exists between these variables, the exposure and outcome. If a covariate was found to be a confounder for the association to the outcome, it was included in the model. In the end, based on assessment of confounders as well as theory, we ended up with a model containing age, as well as the following lifestyle factors: BMI, education levels, alcohol consumption, smoking, physical activity and number of children. Of these, alcohol, number of children and BMI were the only variables not reaching the 5% confounding level but were included in analysis, nevertheless based on theoretical knowledge.

The Kaplan-Maier estimator was used to compare the survival of users and non-users of OC. The log-rank test was used to compare survival curves between groups.

5 Results

This chapter presents all descriptive and analytical results from statistical analysis of the data.

5.1 Descriptive statistics of data

Descriptive data in our selection was divided in distribution of outcome variables, and distribution of other covariates in the selection.

5.1.1 Descriptive statistics of variables

In our population of 126 786 women with information on oral contraceptive use, 51 988 were never users (41.0%) and 74 798 were ever users (59.0%) at last report on oral contraceptive use. Ever users reported a mean 3.0-year duration of use. Compared with never users, ever users were more likely to have smoked. After years of follow-up, we observed 11 310 deaths. The results showed that the mean age for the two outcomes were as follows: For Dead, 48.9 ±8.01 years and for alive, 54.1 ±9.2 years. The mean age for ever users 47.7 ± 7.9 years while the mean age for never users is 51.8 ±8.2 years. The results showed that the average age at inclusion/entry was higher in never-users than ever users. Maximum age at enrolment was 70 years, minimum was 31. Oral contraceptive use (sub-grouped by duration of use) at baseline were distributed as follows: Never user = 41.0%; <1-4 years = 34.8%; 5-9 years = 13.3%; ≥10 years = 10.9%.

The proportion of respondents aged ≥50 years were higher in never users of OC (57.0%) than ever users (38.7%). The average BMI was higher in never users than ever-users of OC, with overweight and obese respondents representing 28.1% and 8.5% of OC users compared to 31.9% and 11.3% of non-users. Duration (years) of education was higher in OC users (13.1 ± 3.5 years) than non-users (12.0 ± 3.5 year). The daily intake of alcohol was higher in users of OC than non-users (4.6 ± 5.5g/day vs. 3.2 ± 4.6g/day). Non-smokers were more prevalent in non-users (43.1%) than users (31.7%) of OC. After adjusting these variables with age, we found Smoking, Physical activity and education were important confounders when assessing the association between OC use and mortality.

Table 5.1 Distribution of covariates according to ever and never users of oral contraceptives (reported as means and s.d, or proportion and total group numbers. Total n respondents and proportion of total study population is reported for each variable):

Characteristics			
	[ALL]	**Never user**	**Ever user**
	N=126 786	***N=51 988***	***N=74 798***
Age (Mean ± SD)	49.4 (8.3)	51.8 (8.2)	47.7 (7.9)
Age			
31 – 40	23 036 (18.2%)	5 705 (11.0%)	17 331 (23.2%)
41 – 50	45 096 (35.6%)	16 629 (32.0%)	28 467 (38.1%)
>=51	58 654 (46.2%)	29 654 (57.0%)	29 000 (38.7%)
Body mass index (kg/m^2) (Mean± SD)	24.7 (4.0)	25.1 (4.2)	24.5 (3.9)
BMI			
Less than 20	8 592 (6.8%)	3 191 (6.1%)	5 401 (7.2%)
20-24	68 345 (54.0%)	26 330 (50.7%)	42 015 (56.2%)
25-29	37 600 (29.6%)	16 598 (31.9%)	21 002 (28.1%)
≥30	12 249(9.6%)	5 869 (11.3%)	6 380 (8.5%)
Years of education (years) (Mean± SD)	12.6 (3.5)	12.0 (3.5)	13.1 (3.5)
Years of education			
< 10	25 628 (20.2%)	14 162 (27.2%)	11 466 (15.3%)
10 - 12	43 212 (34.1%)	17 857 (34.4%)	25 355 (33.9%)
13 – 16	37 180 (29.3%)	13 206 (25.4%)	23 974 (32.2%)
≥17	20 766 (16.4%)	6 763 (13.0%)	14 003 (18.6%)
Daily intake of alcohol(g/d)	4.0 (5.2)	3.2 (4.6)	4.6 (5.5)
Daily intake of alcohol			
Never	23 829 (18.8%)	13 809 (26.6%)	10 020 (13.4%)
0.1 – 4.0	58 715 (46.3%)	24 076 (46.3%)	34 639 (46.3%)
4.1 – 9.9	30 749 (24.3%)	10 117 (19.5%)	20 632 (27.6%)
≥10	13 493 (10.6%)	3 986 (7.6%)	9 507 (12.7%)
Smoking status			
Never	46 164 (36.4%)	22 425 (43.1%)	23 739 (31.7%)
Former	44 149 (34.8%)	16 328 (31.4%)	27 821 (37.2%)
Current	36 473 (28.8%)	13 235 (25.5%)	23 238 (31.1%)
Physical activity	5.7 (1.8)	5.6 (1.9)	5.7 (1.8)
Physical activity			

0 – 3	15 200 (12.0%)	6 479 (12.5%)	8 721 (11.7%)
4 – 7	91 068 (71.8%)	37 005 (71.2%)	54 063 (72.3%)
8-10	20 518 (16.2%)	8 504 (16.4%)	12 041 (16.1%)
Age at first use			
Never user	51 988 (41.0%)	51 988 (100.0%)	NA
< 20	18 165 (14.3%)	NA	18 165 (24.3%)
20 – 24	30 467 (24.0%)	NA	30 467 (40.7%)
25 - 29	13 022 (10.3%)	NA	13 022 (17.4%)
≥30	6 330 (4.9%)	NA	6 330 (8.5%)
Duration of OC use	3.0 (4.6)		3.0(4.6)
Never user	51 988 (41.0%)	51 988 (100.0%)	NA
<1 – 4	44 110 (34.8%)		44 110 (58.9%)
5 – 9	16 811 (13.3%)		16 811 (22.5%)
≥10	13 877 (10.9%)		13 877 (18.6%)
No of children	2.2 (1.2)	2.3 (1.3)	2.1 (1.1)
No of children			
None	11 997 (9.5%)	5 681 (10.9%)	6 296 (8.4%)
1 – 2	69 190 (54.6%)	25 744 (49.5%)	43 446 (58.1%)
3 – 4	42 208 (33.3%)	18 521 (35.6%)	23 687 (31.7%)
≥5	3 441 (2.6%)	2 042 (4.0%)	1 369 (1.8%)
Mortality			
Alive	115, 476 (91.1%)	45 798 (88.1%)	69 678 (93.2%)
Dead	11 310 (8.9%)	6 190 (11.9%)	5 120 (6.85%)
Follow-up time	17.8 (4.4)	17.8(4.6)	17.8 (4.3)

PA grouped "low" – "high".

Daily intake of alcohol measured in grams per day.

Smoking status at enrolment, reported as proportion "never, former, current" smoker.

NA: Not applicable

Physical activity score was slightly higher in OC users, than never user (5.6 ± 1.9 vs 5.7 ± 1.8). Approximately one-third of the respondents of OC use started using OC at < 20 years (24.3%), and close to half of the population started using OC at 20 – 24 years. The average duration of use of OC was 3.0 ± 4.6 years, with 58.9% of the respondents using it for <1 – 4 years. The remaining 22.5% and 18.6% used it for 5 – 9 years and ≥10 years. Regarding mortality, the mortality in non-users was nearly double that observed in OC users (11.9% vs. 6.9%). The

average follow-up duration was not very different between groups, although the result was statistically significant due to the large sample size.

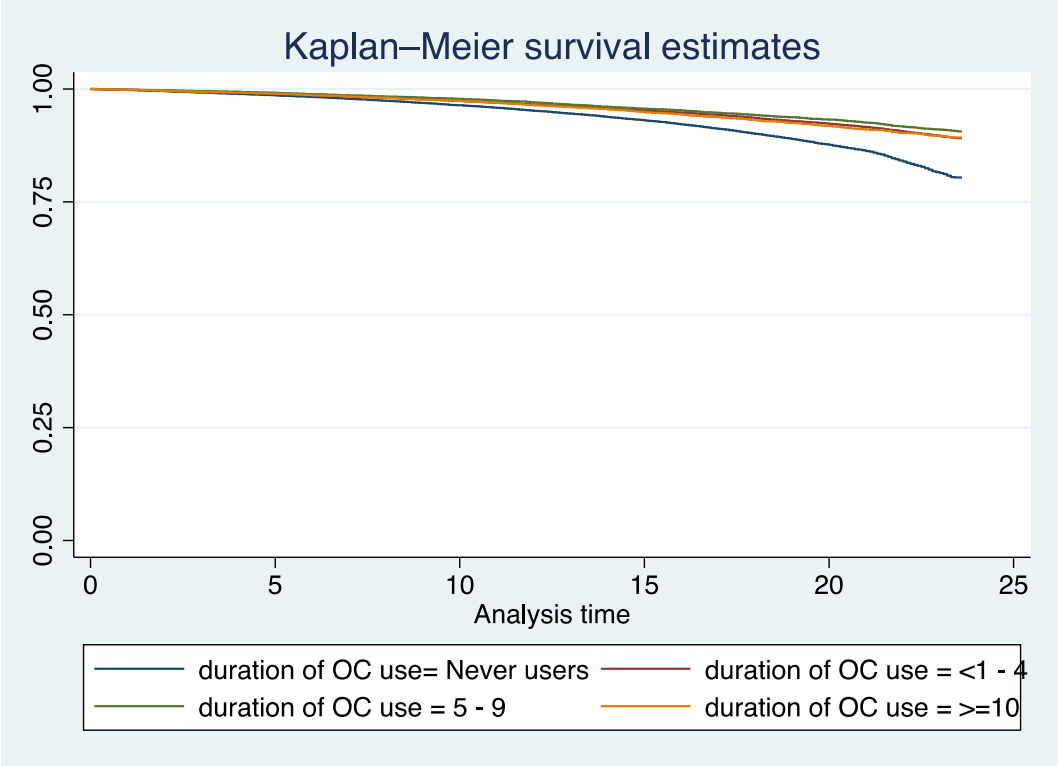

Figure 5.1. Kaplan-Meier estimator for the association between OC use and mortality

5.2 Cox regression analysis

Results for age-adjusted and multivariable adjusted analysis are presented in table 5.2 and table 5.3 respectively below. Never user of OC was used as reference group to which all other OC user groups were compared.

Table 5.2. Hazard ratios (HR) and confidence intervals (CI) in age-adjusted models for duration of oral contraceptive use, age at first oral contraceptive use, and oral contraceptive use on mortality

	HR [95% CI]	p. value	P for trend
Duration of OC use (years):			
Never user			
Ever user (<1-4)	0.96 [0.92-1.00]	0.08	<0.001
(5 – 9)	0.93 [0.87-1.00]	0.04	
(≥10)	0.97 [0.91-1.04]	0.43	
Age at first use of OC (years):			
Never user			
Ever user (<20)	1.01 [0.94-1.08]	0.78	<0.001
(20– 24)	0.94 [0.89-0.99]	0.04	
(25-29)	0.98 [0.92-1.04]	0.50	
(≥30)	0.94 [0.87-1.01]	0.12	
Oral contraceptive use:			
Never user			
Ever user	0.95 [0.92-1.00]	0.03	

Analysis was performed using univariate cox regression and was adjusted for age
HR: Hazard ratio; CI: Confidence interval

Table5.3. Hazard ratios (HR) and confidence intervals (CI) in multivariate adjusted models for duration of oral contraceptive use, age at first oral contraceptive use, and oral contraceptive use on mortality

	HR	[95% CI]	p. value	P for
Duration OC use: Never user Ever user (<1-4)	0.99	[0.94-1.03]	0.75	<0.00
(5 - 9)	0.97	[0.91-1.04]	0.41	
(≥10)	0.97	[0.91-1.05]	0.47	
Age at first use of OC:				
Never user				<0.001
Ever user (<20)	1.00	[0.93-1.08]	0.98	
(20 - 24)	0.98	[0.93-1.03]	0.51	
(25-29)	1.01	[0.95-1.08]	0.69	
(≥30)	0.97	[0.91-1.05]	0.54	
Oral contraceptive use:				
Never user				
Ever user	0.98	[0.95-1.02]	0.5	

Adjusted for age as a continuous variable, alcohol use, smoking, number of children, physical activity, BMI, and education as categorical variables
Analysis was performed using multivariate Cox-regression analysis

5.2.1 Main findings for duration of OC use

Duration of oral contraceptive use is adjusted for age as a continuous variable and presented in the table 5.2 above. Never user of OC is used as reference group to which all other user groups were compared. The analysis shows that the hazard ratios for ever users <1-4 years is 0.96 [CI: 0.92-1.00], 5-9 years is 0.93 [CI: 0.87-1.00], ≥10 years is 0.97 [CI: 0.91-1.04]. Statistical significance is only observed in users between 5 to 9 years and was p = 0.04 in age adjusted model. When adjusted for in the multivariate model as observed in table 5.3, there were no significant HRs where 0.99 (CI: 0.94 – 1.03) for <1-4 years, 0.97 (CI: 0.91 – 1.04) for 5-9 years, and 0.97 (CI: 0.91 – 1.05) for ≥ 10 years of OC use was observed. The HR indicated no association between increasing number of years of OC use levels and mortality

5.2.2 Main findings for age at first Oral contraceptive use

Age at first oral contraceptive use is adjusted for age as a continuous variable and presented in the table 5.2 above. Never user of OC is used as reference group to which all other age groups were compared. The analysis shows that the hazard ratios for ever users age group <20 years is 1.01 [CI: 0.94-1.08], 20-24 years is 0.94 [CI: 0.89-0.99], 25 - 29 years is 0.98 [CI: 0.92-1.04], and ≥ 30 years is 0.94 [CI: 0.87-1.01]. Statistical significance is only observed in users who started OC use between 20 – 24 years and was p = 0.04 in age adjusted model. When adjusted for in the multivariate model (Table 5.3), there were no significant HRs where 1.00 (CI: 0.93 – 1.08) for <20 years, 0.98 (CI: 0.93 – 1.03) for 20 - 24 years, 1.01 (CI: 0.95 – 1.08) for 25 - 29 years, and 0.97 (CI: 0.91 – 1.05) for ≥ 30 years for age at first OC use was observed. The hazard ratio for 20 - 24 years which showed a protective factor in the age adjusted model disappeared in the multivariate adjusted analysis and was no longer statistically significant. The HR indicated no association between increasing age at first oral contraceptive use and mortality.

5.2.3 Main findings for Oral contraceptive use

Oral contraceptive use was adjusted for age as a continuous variable and presented in the table 5.2 above. Never user of OC was used as reference group to which all other ever users were compared. The analysis shows that the hazard ratio for ever users is 0.95 (CI: 0.92 – 1.00). Statistical significance was not observed in the univariate analysis (p 0.5). When adjusted for in the multivariate model (Table 5.3), HR was not significant 0.98 (CI: 0.95 – 1.02) (p=0.5). The HR indicated no association between oral contraceptive use and mortality.

6 Discussion

This study is one of the studies that set out to explore the strength of association between the oral contraceptive use and the risk of mortality (particularly among Norwegian women) using a nationally representative prospective cohort data (NOWAC). The following discussion interprets the results from statistical description and analysis of data, with suggested explanations of results. Identified strengths and limitations in the present study were also assessed, as well as some implications for further research.

6.1 Main findings

The findings of this study validate the hypothesis of no association between the exposure (i.e., Oral contraceptive use) and the outcome (i.e., Mortality). This means that there was no statistical difference in Mortality risk between ever users of Oral contraceptives and never users of oral contraceptives. Furthermore, compared with the different exposure variables such as age at first OC use and duration of OC use, there was still no association between these variables as the exposure and Mortality as the outcome.

Duration of Oral contraceptive use

From the univariate analysis, as the number of years OC was used increased, the age-adjusted analysis showed no association between the duration of Oral Contraceptive use and Mortality. This implies that oral contraceptive users who have used it for many years are not more exposed to a risk of Mortality than those who used it for a lesser number of years. Furthermore, the p-value for trend was statistically significant at <0.001, indicating a trend of no association across the different levels of the duration of Oral contraceptive use. The multivariate analysis also observed that as the duration of exposure to OC use increased, there was still no association between the duration of OC use and Mortality though the result was not statistically significant. However, the p-value for the trend was significant. These results contrast with the study by Charlton et al., 2014 who reported that a longer duration of OC use was more strongly associated with all course mortality (test for trend P=0.02), though overall exposure was not associated with Mortality.

Age at first Oral contraceptive use

In line with the univariate analysis (Table 5.2) performed and adjusted for age, there was a protective factor for OC for participants that started OC use between 20- 24 years. This was also statistically significant. After adjusting for multiple variables, statistical significance was no longer observed, and there was no visible protective factor for starting OC use between ages 20-24. However, these results are not statistically significant. Considering the other categories of age at first use, there was no observed protective or unprotective factor from Mortality. This applies to both the age-adjusted model and the multivariate adjusted model.

Exposure as ever users of oral contraceptives

In the age-adjusted model (Table 5.2), it was observed that there was no relationship between ever users of oral contraception and the Risk of Mortality. This implies that ever users are at the same risk of Mortality when compared to never users. In addition, the results were statistically significant. There was also no relationship observed in the multivariate-adjusted model, and the results were not statistically significant. These results indicate that if a participant has used oral contraceptives for a short period or an extended period, there is no relationship between oral contraceptive use and risk of Mortality.

6.2 Comparisons to other studies

These results for all-cause mortality confirm similar earlier findings by the Royal College of General Practitioners (RCGP) and the Oxford – Family Planning Association. Earlier studies from the Royal College of General practitioners' Oral contraception study suggested a slight increase in all-cause mortality with oral contraceptive use (Royal College of General Practitioners Oral Contraception Study. Lancet 1981). However, further research reported no association or an inverse association (Vessey et al., 1989, Hannaford et al., 2010). The most recent Royal College of General practitioners' Oral contraception study reports examined a subcohort with more detailed information and observed no association (Brind J 2010). These findings are also mainly like the Oxford-Family Planning Association Contraceptive Study, which reported a null finding, whereas a subsequent analysis identified a marginal inverse association (Vessey et al., 2010 Vessey et al., 2003).

In addition, based on the results of our study data for the duration of OC use and age at first use of OC, we observed no increase in all-cause mortality with longer durations of use and

increased age at first use, which is consistent with the trend in the Royal College of General Practitioners' and Oxford-Family Planning Association studies (Vessey et al., 2010, Hannaford et al., 2010).

Several other studies also reported no association between oral Contraceptive use and mortality. Nur et al., 2019 who concluded all-cause mortality showed no association with mortality for OC ever-users among Swedish women, Graff-Iversen et al. (2006), the Nurses' health study by Charlton et al., 2014, Colditz 1994 all concluded that there was no association between oral contraceptive use and risk of mortality.

When performing the multivariate analysis, the HRs for the different duration of OC use was similar in both the age-adjusted and multivariate-adjusted groups. This is suggestive of the fact that the covariates included in this analysis have minimal effect on the association between Oral contraceptive use and mortality.

6.2.1 Descriptive statistics

From the descriptive table 5.1, the largest group of OC users was those reporting duration <1-4 years. The duration of OC use decreased as the number of years increased with the lowest number of women using ≥10 years. Proportion of participant that used OC for the first time between 20- 24 years was highest with 40.7% followed by age <20 which was 24.3%, 25-29 years was 17.4 %, and ≥30 was 8.5%

There was a significant difference in age between groups of never users and ever user, with never user on average 4.1 years older compared to ever users. It follows that oral contraceptive use is more commonly used among younger people.

There was a similar pattern for the distribution of BMI in the selection, with never-users having a BMI on average slightly higher than those women reporting OC use. This put group of never users at an average BMI of 25.1, which was slightly above the threshold for defining overweight (Weir and Jan 2021).

For daily alcohol consumption, women reporting OC use consumed more alcohol compared to never users. We researched studies and could not find an explanation for this relationship between OC users and alcohol consumption however, it could be due to more numbers of OC users compared to never users.

Mean education level was slightly higher among OC users compared to never users. Granted, the difference was only 1.1years between the two, it was statistically significant, and this could be because oral contraceptive use was critical in helping women getting an education as earlier discussed and reported by Daniels et al., 2018.

Proportion of former and current smokers was higher among ever users compared to never user. Lower socioeconomic groups have been termed to have higher prevalence of smoking (Kaczynsky et al., 2008). These results seem conflicting because Oral contraceptive use has been linked to people with an education. Smoking as socioeconomic determinant for poor health has been reported to be mainly among those with lesser education. In this analysis, ever users of OC had higher levels of education hence should have lesser proportion of smokers. However, this is not the case.

6.3 Strengths and limitations

There were a number of possible strengths and limitations associated with our study which were mostly related to the NOWAC study from which data material was obtained, and the type of methodology applied when analyzing. Self-reported data is time-efficient and incurs a lower cost than other forms of measurement and the Nowac study is based on this (Jekel et al., 2014). Because the results of our study depended on what information respondents chose to disclose, so too did the internal validity. External validity depended on whether the selection was representative for that of the source population, namely Norwegian middle-aged women.

6.3.1 Strengths

This study is focused on identifying the strength of association between oral contraceptive use and the risk of Mortality using the Cox proportional hazards model and 95% confidence interval. The key strength of this study is that it draws data from a nationally representative cohort study with complete follow-up; therefore, women participating in the NOWAC study gave an explicit estimation of the association between oral contraceptives and Mortality among Norwegian women. In addition, robust numbers of respondents significantly lowered the chance of random errors affecting the effect estimates from the analysis. The primary exposure, i.e., Oral contraceptive use, duration of Oral contraceptive use, and age at first use of oral

contraceptive estimate the risk of Mortality associated with several years of OC use. The outcome, i.e., Mortality, was confirmed from the Norwegian death registry, which is always well updated using participants' Norwegian personal numbers.

The strength of this study is based on the following additional factors: Given the fact that the sample size was large (N = 126 786), more years of follow-up, the possible confounders (Smoking, Physical activity) were adjusted for, the results from our study can be used to generalize to the female population of Norway in corresponding age groups and can therefore be used as the basis of future hypotheses and development of evidence bases. Furthermore, to aid recall of the type of oral contraceptive used, a photo-booklet of all OCs or hormonal replacement therapy brands was mailed to participants together with a questionnaire. This strengthens this study by preventing the systematic error of recall bias. In addition, Norway had, back in time, restrictive market policies for OCs with a relatively small number of different brands available, thus improving the ability to more rigorously define the exposure in terms of chemical compounds related to different brands. Another strength of this study is that a follow-up questionnaire collected information as recently as 2017, thus providing us with more accurate results for lifestyle factors (physical activity, smoking status, and alcohol consumption) such that people with a change in lifestyle since 2004 could be accounted for and appropriately adjusted.

Another strength of our study was that data from participants had been internally and externally validated. The sample was drawn randomly from the source population. Self-reported data involves an amount of uncertainty regarding the reliability of the information given by respondents (especially on smoking, alcohol consumption, and physical activity). This can be attributed to a self-selection bias in studies based on voluntary participation, giving the "healthy volunteer effect"; however, this has been validated (Lund et al., 2003). According to previously performed studies, the NOWAC study population did not differ significantly from the corresponding age groups of the source population from which it was drawn, except for a slightly higher level of mean education length (Lund et al., 2003).

Mean follow-up time between baseline measurements and the three rounds of follow-up was sufficiently long to allow for the development of outcomes in participants and, therefore, for the detection of risk. The fact that exposure was measured at baseline also gave a particular

temporal indication between exposure and outcomes and could form a causal hypothesis on the relationship between exposure and outcome variables.

6.3.2 Limitations

We identified some possible limitations associated with our study.

As mentioned earlier, there were missing data for some covariates included in our study. Several kinds of bias may be associated with no response for lifestyle data. Missing data on the selected variable in the analysis are reported in figure 4.2. The highest number of missing variables was observed in Physical activity and Alcohol consumption. This was understandable given that some series of the NOWAC study did not include alcohol as a reporting item. The possibilities of bias when reporting lifestyle habits may have skewered the distribution of confounding factors and underestimated their association between oral contraceptive use and the outcome of interest. Reports have found that alcohol is often underreported in studies with self-administered responses. The "social desirability bias" has been shown to cause respondents to not reply correctly regarding alcohol consumption. Respondents tend to underreport and/or underestimate their consumption levels, frequency of drinking, and daily reported consumption (Davis and Vilhena 2010). This means it should be expected that actual alcohol consumption is higher than what is apparent from self-reporting.

We expect that there might be some residual confounding that has not been adjusted for in our analysis, possibly due to the distance in time between baseline and follow-ups or due to other confounding variables having not been included in the analysis.

6.4 Implications for Public Health

Results from this study will contribute to the existing knowledge in the area of reproductive health, stating that there is no risk in mortality for ever-users of oral contraceptives compared to never-users. This could thus allay the fears of women considering oral contraceptive use, and it could also reassure women who took first-generation and second-generation oral contraceptives that this is unlikely to impact their mortality rates. It is both in the general

population's interest and the government to detect causes and risk factors for mortality. Hence, in line with other studies giving the same results, this study would provide more substantial evidence of safe oral contraceptive use.

Future studies should verify the risk of mortality when considering other variables and possible confounders like cancer, cardiovascular diseases, Cerebrovascular diseases, suicide, violence, or accidents. In addition, validation studies can establish the validity of self-reported outcomes by comparing self-reported information with patient journals or possibly by linking oral contraceptive use with the Norwegian prescription database.

6.5 Conclusion

There was no association between oral contraceptive use and mortality in a nationally representative cohort of Norwegian women aged 31-70. In addition, age at first use of oral contraceptive or duration of oral contraceptive use is not associated with the risk of mortality as observed in the Cox regression analysis. This thus would subdue the fear among Norwegian women about the risk of mortality from oral contraceptive use.

Considering the mortality analysis, the advantages of using oral contraceptives for both contraceptive (pregnancy prevention) and non-contraceptive reasons should also be considered. Oral contraceptives help improve ailments like dysmenorrhea, pre-menstrual dysphoric disorder, acne, and symptoms related to fibroid. Oral contraceptives also substantially reduce maternal mortality and also provide protective effects against ovarian cysts and tumors. With the introduction of new contraceptive technologies, it is crucial to understand the effect of exogenous sex steroids in contraceptives to help women make better decisions on their reproductive health.

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KVINNER OG KREFT

1997

KONFIDENSIELT

Hvis du samtykker i å være med, sett kryss for JA i ruten ved siden av
Dersom du ikke ønsker å delta kan du unngå purring ved å sette kryss
for NEI og returnere skjemaet i vedlagte svarkonvolutt.

Hvis du vil være med, så ber vi deg fylle ut spørreskjemaet så nøye som mulig, se orienteringen på brosjyren for nærmere opplysninger.

Med vennlig hilsen

Eiliv Lund
Professor dr. med

24 KK/1997
10.000 46-70 år
261000 – 270999
Skj-type X - 4 sider, hele landet

Jeg samtykker i å delta i spørreskjema-undersøkelsen JA ☐ NEI ☐

Forhold i oppveksten

I hvilken kommune har du bodd lengre enn ett år?

Kommune: **Alder**

1. Fødested: ..... Fra 0 år til ☐ år
2. ..... Fra ☐ år til ☐ år
3. ..... Fra ☐ år til ☐ år
4. ..... Fra ☐ år til ☐ år
5. ..... Fra ☐ år til ☐ år
6. ..... Fra ☐ år til ☐ år
7. ..... Fra ☐ år til ☐ år

Kroppstype i 1. klasse. (Sett ett kryss)

☐veldig tynn ☐tynn ☐normal ☐tykk ☐veldig tykk

Hvor mange års skolegang/yrkesutdannelse har du i alt, ta med folkeskole og ungdomsskole? ..... år

Menstruasjonsforhold

Hvor gammel var du da du fikk menstruasjon første gang? ..... år

Hvor mange år tok det før menstruasjonen ble regelmessig?

☐ Ett år eller mindre ☐ Mer enn ett år
☐ Aldri ☐ Husker ikke

Har du regelmessig menstruasjon fremdeles?

☐ Ja
☐ Har uregelmessig menstruasjon
☐ Vet ikke (menstruasjon uteblitt pga. legemiddelbruk, p-piller, sykdom, trening, annet)
☐ Nei

Hvis Nei;

har den stoppet av seg selv? ..... ☐
operert vekk eggstokkene?..... ☐
operert vekk livmoren? ..... ☐
annet?..... ☐

Alder da menstruasjonen opphørte? ..... år

Graviditeter, fødsler og amming

Fyll ut for hvert barn du har født opplysninger om fødselsår og antall måneder du ammet (fylles også ut for dødfødte eller for barn som er døde senere i livet). Dersom du ikke har født barn, fortsetter du ved neste spørsmål.

Barn	Fødselsår	Antall måneder med amming
1		
2		
3		
4		
5		
6		
7		

Bruk av hormonpreparater med østrogen i overgangsalderen

Har du noen gang brukt hormontabletter/plaster? ☐ Ja ☐ Nei

Hvis Ja; hvor lenge har du brukt hormontabletter/plaster i alt? ..... år

Hvis du har brukt hormonpreparater i *kun 1 år eller mindre;* hvorfor har du brukt midlene så kort tid?

Har nettopp startet behandlingen ☐
Er kvitt plagene ☐
Redd for skadevirkninger ☐
Fikk plagsomme bivirkninger ☐
Annet ..... ☐

Hvor gammel var du første gang du brukte hormontabletter/plaster? ..... år

Hvorfor begynte du å bruke hormontabletter/plaster?

Lindre plager i overgangsalderen (hetetokter, uopplagthet, underlivsplager mm) ☐
Forebygge benskjørhet ☐
Forebygge hjerte/kar sykdom ☐
Annet ..... ☐

Bruker du tabletter/plaster nå? ☐ Ja ☐ Nei

HORMONPREPARAT TIL LOKAL BRUK I SKJEDEN

Har du noen gang brukt hormonkrem/stikkpille? ☐ Ja ☐ Nei

Hvis Ja; hvor lenge har du brukt krem/stikkpille i alt? ..... år

Hvor gammel var du første gang du brukte hormonkrem/stikkpille? ..... år

Bruker du krem/stikkpille nå? ☐ Ja ☐ Nei

UTFYLLENDE SPØRSMÅL TIL ALLE SOM HAR BRUKT ELLER BRUKER HORMONPREPARATER MED ØSTROGEN I FORM AV TABLETTER, PLASTER, KREM ELLER STIKKPILLER

For hver periode med sammenhengende bruk av samme hormonpreparat håper vi du kan si oss hvor gammel du var da du startet, hvor lenge du brukte det samme hormonpreparatet og navnet på dette. Dersom du har tatt opphold eller skiftet merke, skal du besvare spørsmålene for en ny periode. Dersom du ikke husker navnet på hormonpreparatet sett «usikker». For å hjelpe deg til å huske navnet på hormonpreparatene ber vi deg bruke den vedlagte brosjyre som viser bilder av hormonpreparater som har vært solgt i Norge. Vennligst oppgi også nummer på hormon-tabletten/plasteret/kremen/stikkpillen som står i brosjyren.

Periode	Alder ved start	Brukt samme hormon-tablett/plaster/krem/ stikkpille Sammenhengende år	måned	Nr.	Hormontablett/ plaster/krem stikkpille (se brosjyre) Navn
Første					
Andre					
Tredje					
Fjerde					
Femte					

Har hormonpreparatene gitt deg bivirkninger? ☐ Ja ☐ Nei

Hvis ja; kryss av for hvilke bivirkninger:

- Uregelmessige blødninger ☐
- Brystspenning ☐
- Kvalme/magesmerter ☐
- Hodepine ☐
- Hudreaksjoner ☐
- Vektøkning ☐
- Annet ..... ☐

Førte de overnevnte bivirkninger til at du forandret hormonbehandlingen din? ☐ Ja ☐ Nei

Hvis ja;

- Skiftet fra ett hormonpreparat til et annet ☐
- Sluttet på egen hånd? ☐
- Sluttet i samråd med lege ☐
- Annet ..... ☐

Har vekten din økt etterat du begynte å bruke hormoner ☐ Ja ☐ Nei

Hvis ja; Hvor mange kg? .....kg

Informasjonskilder

(Besvares uansett om du har brukt hormonpreparater eller ikke)

Hvor har du skaffet deg informasjon/kunnskap om hormonbehandling?

	Lite viktig	viktig	meget viktig
Allmenpraktiserende lege	☐	☐	☐
Gynekolog	☐	☐	☐
Apotek	☐	☐	☐
Radio/TV	☐	☐	☐
Ukeblader/aviser	☐	☐	☐

Hvilken betydning har råd fra familie og venner hatt? ☐ ☐ ☐

P-Piller

Har du noen gang brukt p-piller, minipiller inkludert? ☐ Ja ☐ Nei

Hvis Ja;

Hvor lenge har du brukt p-piller i alt? .....år

Hvor gammel var du første gang du brukte p-piller? .....år

Hvis du har født barn, brukte du p-piller før første fødsel? ☐ Ja ☐ Nei

Bruker du p-piller nå? ☐ Ja ☐ Nei

Vi vil be deg om å besvare spørsmålene om p-pille bruk mer nøye. For hver periode med sammenhengende bruk av samme p-pille merke håper vi du kan si oss hvor gammel du var da du startet, hvor lenge du brukte det samme p-pille merket og navnet på p-pillene.
Dersom du har tatt opphold eller skiftet merke, skal du besvare spørsmålene for en ny periode. Dersom du ikke husker navnet på p-pille merket, sett usikker. For å hjelpe deg til å huske navnet på p-pille merkene ber vi deg bruke den vedlagte brosjyren som viser bilder av p-pille-merker som har vært solgt i Norge. Vennligst oppgi også nummeret på p-pillen som står i brosjyren.

Periode	Alder ved start	Brukt samme p-pille sammenhengende år	måneder	Nr.	P-pillene (se brosjyren) Navn
Første					
Andre					
Tredje					
Fjerde					
Femte					

Sykdom

Har du eller har du hatt noen av følgende sykdommer?

	Ja	Nei	Hvis Ja: Alder ved start
Høyt blodtrykk	☐	☐	☐
Hjertesvikt/hjertekrampe	☐	☐	☐
Årebetennelse	☐	☐	☐
Blodpropp i legg eller lår	☐	☐	☐
Hjerteinfarkt	☐	☐	☐
Slag	☐	☐	☐
Migrene	☐	☐	☐
Epilepsi	☐	☐	☐
Sukkersyke (diabetes)	☐	☐	☐
Osteoporose	☐	☐	☐
Depresjon (besøkt lege)	☐	☐	☐

Oppfatter du din egen fysiske helse som; (Sett ett kryss)

☐ meget god ☐ god ☐ dårlig ☐ meget dårlig

Oppfatter du din egen psykiske helse som; (Sett ett kryss)

☐ meget god ☐ god ☐ dårlig ☐ meget dårlig

Sosiale forhold

Er du: (Sett ett kryss)

☐ gift ☐ samboer ☐ skilt/separert ☐ ugift ☐ enke

Hvor mange personer er det i ditt hushold?

Antall: .....

Hvor høy er bruttoinntekten i husholdet pr. år?

☐ under 150 000 kr ☐ 151 000–300 000 kr
☐ 301 000–450 000 kr ☐ 451 000–600 000 kr
☐ over 600 000 kr

Røykevaner

	Ja	Nei
Har du noen gang røkt?	☐	☐

Hvis Ja, ber vi deg om å fylle ut for hver aldersgruppe i livet hvor mange sigaretter du i gjennomsnitt røkte pr. dag i den perioden.

	Antall sigaretter hver dag						
Alder	0	1-4	5-9	10-14	15-19	20-24	25+
15-19							
20-29							
30-39							
40-49							
50-59							
60-69							

	Ja	Nei
Røker du daglig nå?	☐	☐

Brystkreft i nærmeste familie

Har noen nære slektninger hatt brystkreft;

	Ja	Nei'	Vet ikke	Alder ved start
datter	☐	☐	☐	☐
mor	☐	☐	☐	☐
mormor	☐	☐	☐	☐
farmor	☐	☐	☐	☐
søster	☐	☐	☐	☐

Undersøkelser for kreft

Hvor ofte undersøker du brystene dine selv?
(sett ett kryss)

Aldri ..... ☐
Uregelmessig ..... ☐
Regelmessig (omentrent hver måned) ..... ☐

Går du til regelmessig undersøkelse av brystene dine med mammografi? (sett ett kryss)

Nei ..... ☐
Ja, med to års mellomrom eller mindre ..... ☐
Ja, med to års mellomrom ..... ☐

Fysisk aktivitet

Vi ber deg angi din fysiske aktivitet etter en skala fra svært lite til svært mye ved 14 og 30 års alder og i dag. Skalaen nedenfor går fra 1-10. Med fysisk aktivitet mener vi både arbeid i hjemmet og i yrkeslivet, samt trening og annen fysisk aktivitet som turgåing o.l. Sett ring rundt det tallet som best angir ditt nivå av fysisk aktivitet.

Alder	Svært lite									Svært mye
14 år	1	2	3	4	5	6	7	8	9	10
30 år	1	2	3	4	5	6	7	8	9	10
I dag	1	2	3	4	5	6	7	8	9	10

Høyde og vekt

Hvor høy er du? ..... cm

Hvor mye veier du i dag? ..... kg

Hvor mye veide du da du var 18 år? ..... kg

Har du lagt på deg etter at du ble 50 år? ☐ Ja ☐ Nei

I tilfelle Ja; hvor mange kg? ..... kg

Solvaner

Dersom du i begynnelsen av sommeren soler deg kraftig, blir huden din; (sett ett kryss)

☐ brun uten først å være rød ☐ rød

☐ rød med svie ☐ rød med svie og blemmer

Etter gjentatt og lenge soling, blir huden din; (sett ett kryss)

☐ dypt brun ☐ brun ☐ lys brun ☐ aldri brun

Hvor mange uregelmessige føflekker større enn 5 mm har du sammenlagt på begge beina (fra tærne til lysken)? Tre eksempler på føflekker større enn 5 mm med uregelmessig form er vist i nedenfor.

☐ 0 ☐ 1 ☐ 2-3 ☐ 4-6 ☐ 7-12 ☐ 13-24 ☐ 25+

Hvor mange små, regelmessige føflekker har du sammenlagt på begge beina (fra tærne til lysken)?

☐ 0 ☐ 1-10 ☐ 11-50 ☐ 51+

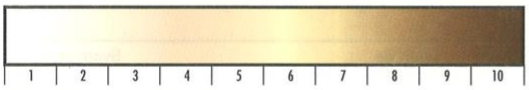
Hvilken øyefarge har du? (sett ett kryss)

☐ brun ☐ grå, grønn eller blanding ☐ blå

Hva er din opprinnelige hårfarge? (sett ett kryss)

☐ mørkbrunt, svart ☐ brun ☐ blond, gul ☐ rød

For å kunne studere effekten av soling på risiko for hudkreft ber vi deg gi opplysninger om hudfarge
Sett ett kryss på den fargen som best passer din hudfarge (uten soling)



Hvor ofte dusjer eller bader du?

	Mer enn 1 g dagl	1 g dagl	4-6 g pr. uke	2-3 g pr. uke	1 g pr. uke	2-3 g pr. mnd.	Sjelden aldri
Med såpe/shampo							
Uten såpe/shampo							

Hvor mange ganger pr. år er du blitt forbrent av solen slik at du har fått svie og blemmer med avflassing etterpå? (ett kryss for hver aldersgruppe)

Alder	Aldri	Høyst 1 gang pr. år	2-3 g. pr. år	4-5 g. pr. år	6 eller flere ganger
Før 10 år					
10-19 år					
20-44 år					
45+ år					

Hvor mange uker soler du deg pr. år i syden?

Alder	Aldri	1 uke	2-3 uker	4-5 uker	7 uker eller mer
Før 10 år					
10-19 år					
20-45 år					
45+ år					

Hvor mange uker pr. år soler du deg i Norge eller utenfor syden?

Alder	Aldri	1 uke	2-3 uker	4-5 uker	7 uker eller mer
Før 10 år					
10-19 år					
20-45 år					
45+ år					

Når bruker du krem med solfaktor (sett evt. flere kryss):

☐ påsken ☐ i Norge eller utenfor syden ☐ solferie i syden

Hvilke solfaktorer bruker du i disse periodene?

	påsken	i Norge eller utenfor syden	solferie i syden
- I dag	.....	.....	.....
- For 10 år siden	.....	.....	.....

Hvilke solkremmerker bruker du? Angi faktor hvis du husker.

	Ja	faktor
Piz Buin	☐	.....
Ambre Solairé	☐	.....
Delial	☐	.....
Natusan	☐	.....
HTH	☐	.....
Cosmica	☐	.....
Andre.....	☐	.....

Hvor ofte har du solt deg i solarium?

Alder	Aldri	Sjelden	1 gang pr. mnd.	2 ganger pr. mnd.	3-4 ganger pr. mnd	oftere enn1 gang pr. uke
Før 10 år						
10-19 år						
20-44 år						
45+ år						

Til slutt vil vi spørre deg om ditt samtykke til å kontakte deg på nytt pr. post. Vi vil hente adressen fra det sentrale personregister. ☐ Ja ☐ Nei

Takk for at du ville delta i undersøkelsen

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