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Review on Hormone Replacement Therapy and its Impact on Morbidity and Longevity

Literature Review

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Literature Review on Hormone Replacement Therapy and its Impact on Morbidity and Longevity

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Chapter 1

A brief introduction to menopause and its treatment

1.1 Menopause

Menopause is a natural process in female's body when the menstruation cycle completely stops, and women are no longer able to get pregnant. Usually, it happens to women at the age of 50 to 55 years, but it can occur early due to surgical hysterectomy, chemotherapy or many other reasons. The average age for women to reach the menopause in the United Kingdom (UK) is 51 years (Bupa, 2018). There are three stages of menopause, such as perimenopause/pre-menopause, menopause, and post-menopause. In perimenopause stage, the menstruation cycle starts to be irregular, and after several consecutive months of irregular periods, it completely stops and eventually women reach the menopausal stage. Most women in the western world suffer from menopausal symptoms. Some of them can be severe and have significant impact on

daily activities. In medical literature, menopause is also termed as climacteric.

1.1.1 Symptoms of menopause

Various symptoms are faced by women who reach menopause, and they vary widely from woman to woman. These symptoms usually start from the perimenopausal stage and can persist up to postmenopausal stage. The common symptoms are hot flashes, night sweats, mood swings, sleep disturbances, vaginal dryness, lack of libido, headache, palpitation, and urinary incontinence. Among these, hot flashes and night sweating are commonly faced by most women, and these symptoms are collectively called vasomotor symptoms. Around 80% of women in the western countries are affected by these menopause-related symptoms (Freeman and Sherif, 2007). Menopause can also increase the risk of developing a number of other medical conditions, such as osteoporosis, dementia, gynaecological cancers, breast cancer, and cardiovascular disease, as the level of female sex hormones, estrogen/oestrogen and progesterone fall sharply after menopause. Before menopause, the risk of getting cardiovascular disease is lower in women than men but it alters after the menopause. The risk of dementia is also higher in women than men after menopause.

1.1.2 Diagnosis of menopause

Usually the signs and symptoms of menopause are sufficient to tell most women that they reached the menopausal transition. However, in some cases, doctors recommend a blood test to women if they are in their 40s, and are suffering from menopausal

symptoms. The blood test measures the hormones called FSH (Follicle Stimulating Hormone) and oestrogen (Mayo Clinic, 2018). FSH level raises and oestrogen level decreases in menopausal women. These tests should not be offered to the women who are taking contraceptives containing oestrogen and/or progestogen because the contraceptives change natural FSH and oestrogen levels in the blood (GP Notebook, 2016). Vaginal pH level test is another effective method to confirm the menopause. The pH level is about 4.5 in vagina during the reproductive years. In menopausal stage, it rises up to 6.0 (Healthline, 2018).

1.1.3 Treatment for menopausal symptoms

There are a number of different hormonal and non-hormonal treatments available to relieve the menopausal symptoms. Among them, Hormone Replacement Therapy is the most common and effective way to treat menopausal symptoms as well as to ameliorate the long term impact of menopause. Some complementary and alternative therapies, such as herbal therapies are also available to treat menopausal symptoms, but there is not enough scientific evidence to support these treatments.

1.2 Hormone replacement therapy in menopause

Hormone replacement therapy (HRT) is a treatment that is commonly used to alleviate troublesome menopausal symptoms. HRT involves replacing estrogen-only or both estrogen and progesterone hormones which are at a lower level as menopause approaches in women. Different types, routes, forms, and preparations of HRT are

used to treat menopausal symptoms depending on the medical conditions and severity of the symptoms. It is also known as menopausal hormone therapy (MHT), estrogen therapy (ET), estrogen replacement therapy (ERT), and hormone therapy (HT).

1.2.1 History of hormone replacement therapy

Hormone replacement therapy has been used for more than 60 years to treat menopausal estrogen deficiency in women. HRT was first available in the 1940s but it was used more widely from the 1960s (Panay et al., 2013). In 1943, estrogen was first available in the market under the name Premarin which is extracted from the urine of pregnant mares (Anderson et al., 2007). At the same time, there are another form of female hormones known as bioidentical hormones, also used for HRT treatment. These hormones are synthesised from soya bean or yam in laboratories and their molecular structures are the same as hormones produced in woman's body (Cirigliano, 2007). HRT was first used in the UK in 1965 (Women's Health Concern, 2017). Following three decades of the use of the estrogen-only for HRT treatment, researchers found that in the absence of progesterone in HRT, women are more likely to develop endometrial hyperplasia which gradually leads to endometrial cancer (Burkman et al., 2001). The combination of estrogen and progesterone therapy was initiated in women who had not received surgical hysterectomy after this finding. These days there is a wide selection of estrogen and progesterone hormone therapy available. The hormones come from both natural extraction and in synthesised form, and under various brand names.

1.2.2 Types and routes of administration of HRT

There are many different kinds of HRT available to treat unpleasant menopausal symptoms. These can be taken orally as tablets or non-orally like transdermal patches, implants, and by many other alternative ways, such as gel, cream, vaginal ring, and injection. HRT comes with estrogen-only or combination of both estrogen and progesterone hormones. Combination of estrogen and progesterone hormones in HRT are known as combined therapy or combined HRT. Types of drugs used in estrogen-only therapy include estradiol, estrone, estriol, 17-β-estradiol, and tibolone. Among these, 17-β-estradiol, estrone, and estriol are the bioidentical form of hormone estrogen. The hormone progestogen is a synthetic version of the hormone progesterone and drug types include dydrogesterone, medroxyprogesterone, norethisterone and levonorgestrel (NHS Choices, 2016). Micronized progesterone is a bioidentical form of the hormone progesterone (Cirigliano, 2007). Estrogen-only HRT is used for women who have had hysterectomy. Combination therapy is used if women have uterus because progesterone safeguards the uterus from endometrial cancer. Estrogen and progesterone are marketed under a large number of brand names in different parts of the world. Examples of major brand names in which estrogen has been marketed include Climara, Climen, Dermestril, Divigel, Estrace, Natifa, Estraderm, Estraderm TTS, Estradot, Estreva, Estrimax, Estring, Estrofem, Estrogel, Evorel, Fem7 (or FemSeven), Menorest, Oesclim, Oestrogel, Sandrena, Systen, and Vagifem. For progesterone, the major brand names are Prometrium and Provera. Combined HRT is available under the brand names Activelle, Angelic, Cliane, Femhrt, Prefest, Prempro, Climara pro, Com-

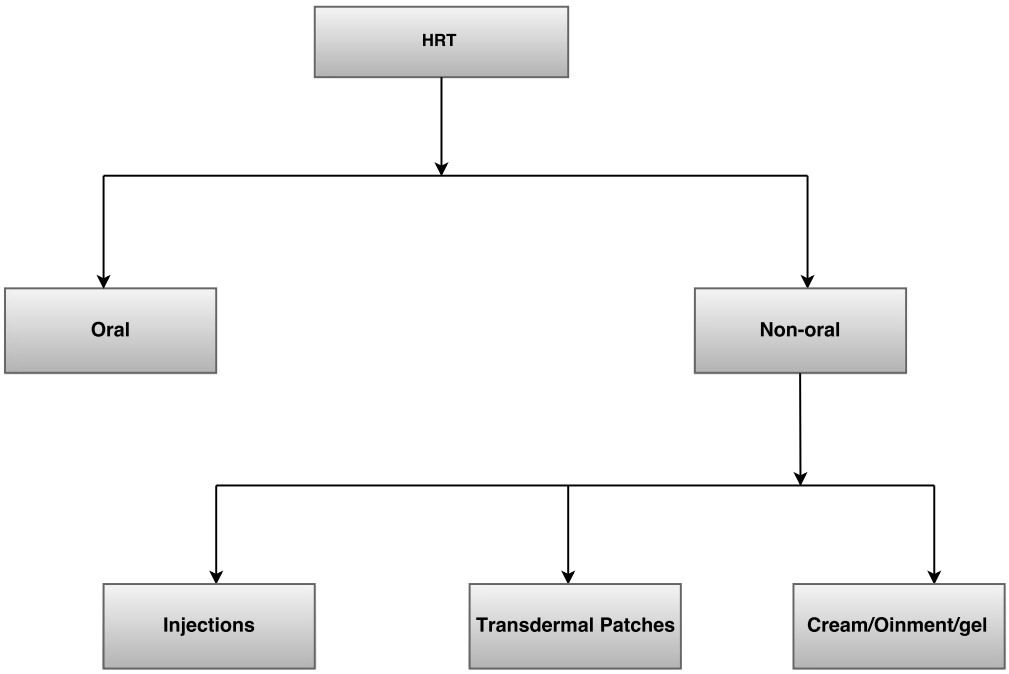

Figure 1.1: *Different routes of administration of Hormone Replacement Therapy*

bipatch, Estalis, Eviana, Evorel Conti, Evorel Sequi, Kliogest, Novofem, Sequidot, and Trisequens (FDA, 2018).

It is important to consider which type of HRT is good for an individual to get the best outcome from the therapy. Treatment should be prescribed according to patients' symptoms, age, and any medical conditions. In Figure 1.1, we draw a flow chart of different routes of administration of hormone replacement therapy. In Table 1.1, we list different classes of HRT, their trade names, and the other drugs available in the same class. Table A.1 presents the brand and generic names of different drugs class along with their routes of administration.

Table 1.1: *Different classes of drugs used for hormone replacement therapy*

Drug class	Trade name	Other drugs in the same class
Estrogen/Oestrogen	Conjugated Equine Estrogen (CEE)	Estradiol/Oestradiol
	Conjugated Estrogen (CE)	Estriol
	Premarin	Estrone
		Tibolone
		17-β-estradiol
Progesterone	Progestogen/Progestin	Dydrogesterone
		Medroxyprogesterone
		Norethisterone
		Levonorgestrel
		Micronized progesterone

Table 1.2: *Routes of administration of different classes of drugs used for HRT and their brand names*

Routes of administration	Generic name	Brand name
Oral tablets	Estrogen-only:	
	Estradiol	Estrofem
	Estradoil acetate	Femtrace
	Estradoil valerate	Progynova
	Micronized estradiol	Estrace
	Progesterone-only:	
	Micronized progesterone	Prometrium
	Medroxyprogesterone acetate	Provera
	Combination of both:	
	Estradiol/Norethindrone acetate	Activella

Continued on next page

Table 1.2 – *Continued from previous page*

Routes of administration	Generic name	Brand name
	Estradiol/Drospirenone	Angeliq
	Ethinyl estradiol/	Femhrt
	Norethindrone acetate	
	Estradiol/Norgestimate	Prefest
	Conjugated estrogen/	Prempro
	Medroxyprogesterone	
Transdermal patches	Estrogen-only:	Alora
	Estradiol	Climara
		Minivelle
		Vivelle
		Vivelle-Dot
		Menostar
		Estraderm
	Combination of both:	
	Estradiol/Levonrgestrel	Climara Pro
	Estradiol/Norethindrone acetate	Combipatch
Topical gels	Estrogen-only:	Estrogel
and oinments	Estradiol	Estrasorb
	Estropipate	Rontagel
	Conjugated estrogens	Divigel
		Elestrin
Nasal sprays	Estrogen-only:	Aerodiol
	Estradiol	
Injections	Estrogen-only:	
	Estradiol valerate	Delestrogen
	Estradiol undecylate	Progynon Depot
	Polyestradiol phosphate	Estradurin
	Estradiol cypionate	Depo-Estradiol
Vaginal ring	Estrogen-only:	

Continued on next page

Table 1.2 – *Continued from previous page*

Routes of administration	Generic name	Brand name
	Estradoil	Estring
	Estradoil acetate	Femring

1.3 Risks and benefits of using HRT

To date, numerous research has been carried out to establish the mortality/ longevity and morbidity risks of HRT treatment as well as to investigate its effect on various diseases. However, there is still uncertainty regarding the risks and benefits of its use. Most studies related to HRT are regional, observational, and considered a small number of participants (Brenner et al., 1994; Christiansen, 1996; Ettinger et al., 1996; Cass and Runowicz, 1998; Zandi et al., 2002; Hodis et al., 2003; Schuetz et al., 2007; Anderson et al., 2007; Freeman and Sherif, 2007; Schierbeck et al., 2012). The Heart and Estrogen/Progestin Replacement Study (HERS) was the first randomised, double blinded, placebo control trial that evaluated the outcome of combined HRT on cardiovascular events in 2,763 postmenopausal American women who have had prior history of coronary heart disease (CHD) (Wells and Herrington, 1999). They found 179 women in the hormone group, and 182 women in the placebo group who suffered either a non-fatal myocardial infarction or CHD death (Relative Risks (RR)= 0.99; 95% confidence interval (CI), 0.81-1.22). In 1993, the Women's Health Initiative (WHI) set up a randomised, placebo control trial in the United States of America (USA) to examine the risks and benefits of both estrogen-only and combined HRT

among postmenopausal women (Women's Health Concern, 2017). This is considered one of the biggest clinical trials in HRT history. Another largest observational study, the Million Women Study (MWS) comprising more than one million women in the UK was set up in 1996 to investigate the effects of HRT on breast cancer incidence and death (Emily et al., 2003). A publication from the WHI in 2002 opposed the use of HRT after finding that HRT increases the incidence of breast cancer (Rossouw et al., 2002). In 2003, MWS also raised concern regarding the safety of HRT (Emily et al., 2003). As a result of these two major studies, HRT user count decreased from 2 million to less than 1 million in the UK between 2002-07 (Women's Health Concern, 2017). However, rigorous investigations are required to confirm these results since a number of flaws in the design of these two studies have been found. A Bayesian meta-analysis by Salpeter et al. (2009) comprising 19 randomised control trials and 8 observational studies on HRT and mortality in 228,171 younger postmenopausal women indicates an overall reduction of mortality in HRT user compared to life-time non-user. Their findings show that a treatment starting shortly after menopause and its long term continuation may prevent a number of diseases such as osteoporosis, atherosclerosis, and reduce mortality. A recent analysis of WHI shows that HRT was not associated with risk of all-cause, cardiovascular, or total cancer mortality during a cumulative follow-up of 18 years (Manson et al., 2017). The risks of morbidity and mortality in women undertaking hormone replacement therapy may vary depending on their age, individual health conditions, and the doses they are taking. Careful consideration of individual health condition is necessary before prescribing HRT treatment. Therefore,

further research is crucial to clearly understand how HRT affects younger and older postmenopausal women, to provide a better treatment and good quality of life for them after menopause.

In Chapter 2, we provide findings of several studies published over time on HRT on all-cause, and cause-specific mortality. These findings will give us a glimpse on the pattern and current state of use of HRT and its impact on women, and in particular in the UK.

Chapter 2

Review on existing HRT research

In this chapter, we first describe the design and settings of some major studies that investigated the risks and benefits of HRT use. Then we outline some of the previous research findings on HRT and its impact on various diseases.

2.1 Major studies on HRT

In this section, we outline the three largest studies on HRT on women's health: the Women Health Initiative Study, the Million Women Study, and the Nurses' Health Study which were highlighted in most HRT related research. We provide the results from these studies in later sections of this chapter.

2.1.1 Women's Health Initiative Study

The Women's Health Initiative (WHI) study is a large and long term national health study focused on assessing some of the most common causes of mortality and morbid-

ity among American postmenopausal women, including cancer, cardiovascular disease, and osteoporotic fractures. Set up in 1993, the WHI enrolled 161,808 healthy postmenopausal women of age 50−79 into three randomised control trials (RCTs) and an observational study (OS) at 40 US clinical centres (WHI Organization). RCTs consisted of three separate trials: Hormone Therapy, Calcium/Vitamin D, and Dietary Modification trial (Anderson et al., 1998). In Hormone Therapy trial, WHI enrolled 27, 347 women to investigate the risks and benefits of receiving conjugate equine estrogen (CEE) and CEE plus medroxyprogesterone acetate (MPA) therapy on coronary heart disease (CHD), bone fractures and breast cancer. Treatment group was provided daily oral CEE (0.625 mg)-alone or in combination with MPA (2.5 mg). In Calcium/Vitamin D and Dietary Modification trial, WHI enrolled 36,282 and 48,835 participants respectively. There were 68,132 women in total who participated in randomised control trials. Observational study consisted of 93,676 postmenopausal women in total. All participants from the Calcium/Vitamin D trial also participated in Dietary Modification trial. 8,050 women participated in both Hormone Therapy and Dietary Modification trial. At the end of the initial study period in 2005, WHI Extension Studies (2005-2010, 2010-2020) continued follow-up of all women who consented (WHI Organization). Figure 2.1 is extracted from WHI Organization which shows the numbers of the participants of different groups in the trial.

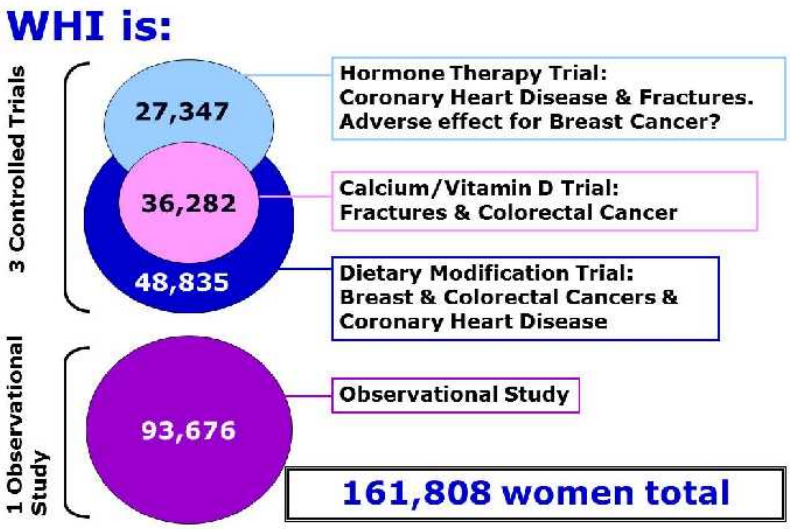

Figure 2.1: *Design and participants of WHI clinical trial.*

Source: https://www.whi.org/SitePages/WHI%20Home.aspx

2.1.2 The Million Women Study

The Million Women Study (MWS), a multi-centre, population based prospective cohort study was set up in the UK between 1996 and 2001 to investigate the effects of HRT on women's health and specifically, on the incident and fatal breast cancer. The MWS invited women aged 50−64 years to attend at 66 national health service breast screening centres, and to participate in the study. Women received a study questionnaire at these centres, which they were asked to complete and return at the time of breast screening. Around 70% of those attending the programme returned the questionnaires and agreed to take part in the study (University of Oxford). Over 1.3 million women enrolled in the study during the study period. Approximately, one in every four women in the UK participated in the study, and this marked MWS as the world's largest observational study of its kind.

2.1.3 The Nurses' Health Study

The nurses health study (NHS), a large prospective cohort study in the USA, began in 1976 with an aim to investigate the association of diet, smoking, physical activity levels, obesity, oral contraceptive use, hormone therapy, endogenous hormones, dietary factors, and other behaviors and characteristics with various chronic diseases in women. The study is divided into three cohorts: NHS original cohort, NHS II, and NHS 3 (Harvard School of Public Health). It recruited registered nurses of ages 30−55 years from across the different states of America to respond to a set of baseline questionnaires. The NHS original cohort started in 1976 and it consisted of 121,700 married women. The NHS II cohort began in 1989 with 116,430 single and married women of ages 25−42. The NHS 3 cohort started in 2010 and it adds licensed practice nurses and licensed vocational nurses to NHS II cohort. The enrolment of NHS 3 cohort is currently open. From the beginning of NHS original cohort to NHS 3, more than 280,000 participants enrolled in the programme.

2.2 HRT and its impact on longevity

There are numerous observational studies and randomized control trials that investigated the all-cause and cause specific mortality among the HRT users. Most of the studies took place in the developed countries, and majority of them were in the USA and UK. A significant number of studies took place in other European countries, such as Finland, Denmark, Sweden, the Netherlands, Poland, and Italy. However, results from these studies on HRT and longevity are inconsistent. Hunt et al. (1990)

studied a longitudinal cohort of 4,544 females of age 45−54 in England and Wales who used long-term opposed or unopposed HRT. Participants were monitored until death, paying particular attention to cardiovascular mortality, death from breast and endometrial cancer, and death attributed to suicide and suspected suicide. Their results showed that overall mortality was significantly lower than expected among HRT users compared to national mortality rate (RR= 0.56; 95% CI, 0.47-0.66). When specific causes of death were considered, the higher mortality rates were those for injury, poisoning and violence, and for suicide and suspected suicide (RR= 1.54; 95% CI, 1.02-2.06 and RR= 2.40; 95% CI, 0.68-3.11 respectively). Folsom et al. (1995) performed a prospective cohort study on 41,070 postmenopausal Iowa women aged 55−69 who were followed up for 6 years, and founds reduced risk in all-cause mortality (RR= 0.78; 95% CI, 0.65-0.94). A meta-analysis of thirty randomized control trials consisting of 26,708 participants performed by Salpeter et al. (2004) investigated all-cause deaths and deaths due to cardiovascular disease, cancer, or other causes of mortality in younger and older postmenopausal women. Their findings showed that HRT reduced mortality in the younger age group (Odds ratio (OR) = 0.61; 95%CI, 0.39-0.95), but not in the older age group (OR= 1.03; 95%CI, 0.90-1.18). For all ages combined, HRT did not significantly affect the risk for cardiovascular or cancer mortality, but reduced mortality from other causes (OR = 0.67; 95%CI, 0.51-0.88). Persson et al. (1996) conducted a cohort study of cancer incidence and mortality in 22,597 Swedish women receiving estrogen and estrogen-progestin replacement therapy who were followed up for thirteen years. Their findings reveal that, the use of combined therapy was as-

sociated with an increasing relative risk of breast cancer (RR=1.4; 95% CI, 1.1-1.8). The relative risk of endometrial cancer was substantially increased, with the highest RR of 5.0 and 95% CI, 1.6-5.9 in women prescribed estrogen-alone, whereas those given combined therapy showed no elevation in risk. HRT reduces overall mortality by 30% when started in young postmenopausal women who are less than 60 years old and continued for a long-term period (Hodis and Mack, 2014). A Bayesian meta analysis of 19 randomized control trial and and 8 observational studies conducted by Salpeter et al. (2009) also found that HRT decreases the mortality rate for younger postmenopausal women. Their study concur with the Nurses' Health Study performed by Grodstein et al. (1997). Grodstein et al. (1997) also reported that current hormone user with coronary risks factor had the largest reduction in mortality (RR=0.51; 95% CI, 0.45-0.70). Boardman et al. (2015) performed a meta-analysis consisting 19 randomised control trials of 40,410 postmenopausal women to observe the effects of oral HRT for preventing cardiovascular disease. They find no protective effects of HRT for all-cause mortality, cardiovascular death, non-fatal myocardial infraction, angina, or revascularisation. The impact of any kind HRT on the risk of mortality may change depending on many factors such as individual the health condition, specific disease, family history of any kind of cancer etc. So, health professionals should give careful consideration before prescribing different HRT.

2.3 Effect of HRT on various diseases

Numerous observational studies as well as a large number of randomised control trials has been carried out to find the effects of HRT on several life threatening diseases. Majority of these studies focused on morbidity and mortality of a specific disease associated with HRT. Here, we provide a literature review on the impact of HRT on various chronic diseases. In the following discussion, We only consider studies comprising sample sizes greater than or equal to 8,000. All of the studies selected for this literature review on HRT are summarised in the Appendix A.

2.3.1 Osteoporosis

Osteoporosis is a condition that decreases the bone mass density and makes bone more fragile. It is one of the most common causes of morbidity and mortality in post-menopausal women in the western countries. Due to estrogen deficiency, bone density decreases sharply in women and causes significant amount of bone loss during the post-menopausal years. This is why the risk of developing osteoporosis is higher in women as they approach the menopause (Gauthier et al., 2011). People with osteoporosis are facing most common injuries like wrist fracture, hip fracture and fractures of the vertebrae. According to the national health records, the number of postmenopausal women living with osteoporosis in the UK was 1.8 million in 2010. Gauthier et al. (2011) predicted that the number will increase to 2.1 million by 2020. They use osteo-porotic data from 2010 and using 1-year cycle Markov model, forecast the numbers up to 2020. A report published by the International longevity Centre (ILCUK, 2010) on

the current management of postmenopausal women aged 55 or over in the UK shows the following alarming results:

- Overall, the number, rate and cost of fractures among women of this age group is rising;
- The level of hospital stays has increased from approximately 78,000 in 2004/05 to 88,000 in 2008/09, an increase of 13%;
- Adjusting these figures for population size, the level of hospital admissions has increased from 10.4 per 1,000 population in 2004/05 to 11.4 per 1,000 population in 2008/09;
- The tariff cost has risen from approximately £390 million in 2005/06 to over £430 million in 2008/09;
- The total cost to the NHS of hospital stays alone is in excess of £400 million per year for women in this age group;
- Nearly 10% of women aged over 55 years who go into hospital with a fracture die while they are an in-patient − this equates to around 6,000 deaths per year;
- There is significant regional variation in levels of fracture admissions for women.

Several epidemiological studies have shown that long term use of HRT provides protection against bone fractures (Christiansen, 1996; Cauley et al., 2003; Salpeter et al., 2009). A WHI trial of estrogen plus progestin showed 34% reduction in hip and clinical vertebral fracture and 24% reduction in total osteoporotic fractures (Manson et al.,

2013). Further analysis from WHI trial showed an overall 33% hip fracture decrease in women who received the CEE plus MPA and CEE-alone compared with the placebo group (Manson et al., 2017). A significant fracture benefit persisted over thirteen years for women assigned to CEE plus MPA group in the WHI trial (Hazard Ratio (HR)= 0.81, 95% CI, 0.68-0.97).

2.3.2 Dementia

Dementia is a chronic cognitive disorder that affects communication and performance of daily activities. Alzheimers disease (AD) is the most common form of dementia, causing 60%−80% of all dementia cases (Alzheimer's Associations). It specifically affects parts of the brain that control thought, memory and language. Older women are at a greater risk of Alzheimer disease than men due to postmenopausal estrogen deficiency (Zandi et al., 2002). Over the past two decades, a number of observational studies (Henderson et al., 1994; Paganini-Hill and Henderson, 1994, 1996; Kawas et al., 1997; Baldereschi et al., 1998; Zandi et al., 2002), randomized control trials (Mulnard et al., 2000; Wang et al., 2000) and a few meta-analyses (LeBlanc et al., 2001; Henderson, 2014) have been carried out to examine the relationship between HRT treatment and the risk of developing AD. Many of the observational studies suggested that early initiation after menopause and long term use of HRT delays the onset of AD (Paganini-Hill and Henderson, 1996; Kawas et al., 1997; Baldereschi et al., 1998). But a meta-analysis of nine randomized clinical trials of estrogen conducted by Henderson (2014) founds no improvement in cognitive symptoms in AD women who received

HRT. Some research also found adverse effect of HRT treatment in women with AD (Mulnard et al., 2000). However, most of these studies considered only a small number of participants. Thus, the impact of HRT on dementia is not clear. Imtiaz et al. (2017) conducted an observational study on postmenopausal hormone therapy and Alzheimer disease in Finland. Their study comprised 8,195 women of ages 47−56 who were followed up for 20 years. They found that postmenopausal estrogen use was not associated with AD risk in register-based or self-reported data (HR= 0.92, 95% CI, 0.68-1.2 and HR=0.99, 95% CI, 0.75-1.3 respectively). A subgroup study, known as WHI Memory Study (WHIMS) enrolled women from WHI estrogen plus progestin trial to evaluate the effect of HRT on the incidence of dementia and mild cognitive impairment compared with placebo (Shumaker et al., 2003). Their report showed that combined HRT increased the risk of dementia in postmenopausal women aged 65 years or older. They enrolled 4,532 healthy postmenopausal women who were free of probable dementia and aged 65 years and older for the study. Probable dementia as defined in their study included Alzheimer's disease (AD), vascular dementia (VaD) and mixed types (both AD and VaD). After an average four years of follow up, the study found that overall 61 women were diagnosed with probable dementia. Among them 40 (66%) in the estrogen plus progestin group and 21 (34%) in the placebo group. The hazard ratio for probable dementia was 2.05 (95% CI, 1.21-3.48; P = .01). At the same time, another WHI subgroup study on 2,947 hysterectomized women aged 65−79 years evaluated the effects of daily CEE (0.625 mg)-only on the incidence of probable dementia (Shumaker et al., 2004). After an average follow-up of 5.2 years, the study found that

the relative risks of probable dementia for CE-alone versus placebo was 1.49 (95% Cl, 0.83-2.66). The absolute risk of probable dementia for CEE plus MPA versus placebo was 45 versus 22 cases, and for CEE-alone versus placebo the risk was 37 versus 25 cases per 1000 women-years. Results from the studies on HRT on dementia appears that late initiation of HRT may be detrimental for dementia.

2.3.3 Cardiovascular disease

Cardiovascular disease (CVD) is a group of disorders related to the heart and blood vessels. CVD mainly includes coronary heart disease (CHD), stroke, transient ischaemic attack, peripheral arterial disease, heart attack, deep vein thrombosis, and pulmonary embolism. There are an estimated 3.5 million women living with CVD in the UK, with around 78,000 dying from conditions such as heart attack and stroke each year, accounting for a quarter of all female deaths (British Heart Foundation, 2016). CVD kills more than twice as many women as breast cancer in the UK. It is believed that oestrogen helps to reduce the formation of fatty-plaques in women's heart. So, after menopause, women are more likely to develop cardiovascular disease than men. Menopause can also cause palpitations in the heart due to the reduction of female hormones. An observational study conducted by Gast et al. (2011b) showed that women with vasomotor symptoms have an increased risk of CHD. Most of the observational studies suggest that HRT may have beneficial effects in lowering the risk of cardiovascular events among postmenopausal women (Grodstein et al., 1994; Grodstein and Stampfer, 1995; Grodstein et al., 1997; Boardman et al., 2015). However,

results from the randomised control trials showed mixed results (Hulley et al., 1998; Hodis et al., 2003; Schierbeck et al., 2012). Some studies showed that HRT may protect women from cardiovascular disease if started around the time of menopause (Hodis and Mack, 2014), but initiation after 10 years of menopause could be harmful (Hulley et al., 1998). Gast et al. (2011a) pooled data from a Dutch and Swedish population-based sample of 10,787 women of age 46 to 64 years who were free of CVD at baseline to study the effect of HRT on CVD. However, they did not find any associated risk of CVD in HRT user compared to non-user. Grodstein and Stampfer (1995) found that women who are receiving HRT treatment currently are at 50% lower risk of occurring CHD than a never user. However, WHI study failed to show any relation between HRT and CHD through their large randomised, double blinded, and placebo control trial (Manson et al., 2013). The Heart and Estrogen/Progestin Replacement Study (HERS), a randomised, double-blinded, placebo control trial on combined HRT also found no overall reduction in risk of CHD events among postmenopausal women with CHD (Hulley et al., 1998). A recent systematic review conducted by Boardman et al. (2015) to assess the effects of oral hormone therapy for preventing cardiovascular disease included 19 randomised trials consisting 40,410 postmenopausal women in total. Their findings showed that HRT conferred no protective effects for all-cause mortality, cardiovascular death, non-fatal myocardial infraction, angina, or revascularisation. They also found an increased risk of stroke in the HRT users compared to non-users (RR=1.24, 95% CI, 1.10-1.41). Thus the risks and benefits of HRT on CVD have not been fully understand so far.

2.3.4 Breast cancer

The use of HRT and the incidence of breast cancer is controversial. Several studies have been carried out to investigate the impact of HRT on breast cancer incidence and most of the outcomes do not support the use of HRT (Manson and Martin, 2001; Manson et al., 2013). However, it is still not clear how estrogen and progesterone hormone causes breast cancer. In 2002, the WHI trial reported that combined HRT increased the risk of breast cancer among women by 26% (Rossouw et al., 2002). However, further reports of WHI indicate that CEE alone decreased the risk of breast cancer by 23% (Manson et al., 2013). The MWS, showed that current use of HRT increases the incidence of breast cancer (Emily et al., 2003). They reported that use of HRT reduces the sensitivity of mammography and hence increases the probability that a breast cancer is diagnosed as an interval rather than a screen detected cancer. Their findings also showed that risk was substantially greater for combined HRT. Their results are based on 517 deaths in women who had no history of breast cancer at recruitment. Another study showed that estrogen alone does not increase the risk of breast cancer if taken for 5−7 years and women initiating therapy ten or more years after the menopause experience a 23% reduction in risk (Stefanick et al., 2006). However, a recent study based on a randomised control trial of 1,006 healthy Danish women of ages 45−58 undertaking combined hormone therapy concluded early initiation and prolonged HRT did not result in an increased risk of breast cancer (Schierbeck et al., 2012). It is known that many breast cancer incidence is related to obesity and the previous family history of the occurrence. So, before prescribing HRT, these should be taken into account.

2.3.5 Endometrial cancer

Endometrial cancer is also known as uterine or womb cancer. According to the World Health Organization's report 2014, approximately 320,000 women are diagnosed with endometrial cancer worldwide each year and 76,000 die, making it the sixth most common cancer in women (McGuire, 2016). The occurrence has risen alarmingly over the last two decades in the UK. There was an increase of over 40% in endometrial cancer incidence in the UK between 1993 and 2013 (Galaal et al., 2014). It appears most frequently in women during perimenopause or after menopause because of insufficiency of the female hormones. There is also an higher risk of endometrial hyperplasia in women who use unopposed estrogen therapy. A meta-analysis of 30 observational studies assessed the use of estrogen-only HRT on the risk of developing endometrial cancer (Grady et al., 1995). There was an increased risk of endometrial cancer among unopposed estrogen users compared with non-users (RR= 2.3, 95% CI, 2.1-2.5). Prolonged duration of use further increased the risk with RR=9.5. However, their analysis did not show the statistically significant risk of mortality from endometrial cancer (RR= 2.7, 95% CI, 0.9-8.0). Persson et al. (1999) investigated the risk of developing endometrial cancer after replacing estrogen and progesterone hormone on 8,438 Swedish women. These women were followed up through time to time questionnaire from 1987−1993. Their findings showed that the risk of invasive endometrial cancer increased fourfold in women using estrogen-alone for six years or longer (RR = 4.2; 95% CI, 2.5-8.4). Women receiving combined HRT for the same time period had a lower and non-significant risk (RR = 1.4; 95% CI, 0.6-3.3). Considering the results

from the studies on HRT and endometrial cancer, it seemes that the women without hysterectomy should not be prescribed unopposed estrogen.

2.3.6 Ovarian cancer

Ovarian cancer is the seventh-most common cancer in women and the eighth-most common cause of death from cancer (WHO, 2014). This usually affects women who are above the age of 50 and have been through the menopause but sometimes it can also affect younger women due to radical surgery or genetic history in the patient's family. Ovarian cancer is more common in Europe and North America than in Africa and Asia (WHO, 2014). A cohort study in the US on HRT use, and the risk of ovarian cancer comprising 44,241 postmenopausal women showed an adverse effect of HRT on ovarian cancer (Lacey Jr et al., 2002). After a time dependent analysis adjusted for age, menopause type, oral contraceptive use, ever use of estrogen-only they found significant association of HRT with ovarian cancer (RR=1.6; 95% Cl, 1.2-2.0). They also found that the increasing duration of estrogen-only use was highly associated with ovarian cancer. They did not have information on whether HRT included progenterone. An observational study conducted by Folsom et al. (2004) on ERT and ovarian cancer among 31,381 postmenopausal women in Iowa also showed an elevated risk of ovarian cancer compared to never user (RR=1.7; 95% Cl, 1.1-2.8). However, a collaborative analysis in the US included 12 case-control studies consisting 2,197 cases and 8,893 controls, did not find an excess risk (RR= 0.9; 95% CI, 0.7-1.3 in hospitalbased studies and RR=1.1; 95% CI, 0.9-1.4 in population-based studies)(Harris et al., 1992). Further

analysis is needed to established the actual benefits of HRT in developing ovarian cancer.

2.3.7 Lung cancer

Lung cancer is a commonly diagnosed and serious type of cancer and a leading cause of mortality in women. Women are more prone to developing lung cancer than men and it kills more women each year than breast cancer, uterine cancer, and ovarian cancer combined. Even though it is believed that smoking is the number one cause of lung cancer in women, a higher percentage of women who develop lung cancer are life-long non-smokers (Verywellhealth). In 2011, about 19,700 women were diagnosed with lung cancer in the UK, making it the second most common cancer diagnosed in women after breast cancer (NHS Choices, 2015). However, there is not enough research carried out for HRT and lung cancer compared to other diseases such as dementia, breast cancer, osteoporosis, and cardiovascular disease. A population-based, cohort study on Swedish women performed by Adami et al. (1989) first demonstrated that lung cancer risks increased in women receiving HRT. A secondary analysis from the WHI has found that past use of hormone replacement therapy with estrogen plus progestin increases the risk of dying from lung cancer for women who develop the disease (Hampton, 2009). This analysis examined the incidence of non-small cell lung cancer and mortality during 5.6 years of intervention with HRT or placebo, and continued 2.4 years of additional follow-up. The study has found that mortality after a lung cancer diagnosis was significantly higher in those who received combined hormone therapy. But a recent meta analysis

performed by Yao et al. (2013) of twenty-five studies consisting 656,403 participants showed a reduced lung cancer risks in females receiving HRT treatment (OR= 0.91; 95%CI= 0.83-0.99, P value= 0.033). Their study found that HRT decreases lung cancer risks in the patients with BMI$< 25kg/m^2$ and never smoker (OR=0.65 and OR=0.86 respectively). Their study also concluded that HRT with artificial menopause could increase the risk of lung cancer. Thus the role of hormone replacement therapy in developing lung cancer is still unclear and needs further analysis .

2.3.8 Colorectal cancer

Colorectal cancer, often known as bowel or colon cancer is considered the third leading cause of cancer incidence and death in women, after breast and lung cancer (Cokkinides et al., 2005). The occurrence of colorectal cancer begin to rise as women approach their mid-40s and continue to rise into old age (Burkman et al., 2001). According to estimates for 2015, there were 18,700 new cases of colorectal cancer and 7,300 deaths resulting from colorectal cancer in women in the United Kingdom (Cancer Research UK, 2015). Grodstein et al. (1999) conducted a meta-analysis on postmenopausal HRT use and colorectal cancer, comprising 18 epidemiological studies. Their study found a 20% reduction in the risk of colon cancer in HRT users compared to never users (RR = 0.80; 95% CI, 0.74 - 0.86). A 34% reduction in the risk of colorectal cancer was found in the current HRT users in their studies (RR = 0.66, 95% CI, 0.59 - 0.74). The total duration of HRT use did not appear to affect the risk of colon cancer. A cohort study by Calle et al. (1995) on 422,373 postmenopausal and cancer

free women in America found significantly decreased risk of fatal colon cancer (RR = 0.71; 95% CI, 0.61 - 0.83) in women taking estrogen replacement therapy. The reduction in mortality risk was strongest among current ERT users, and there was a significant (P =.0001) trend of decreasing risk with increasing years of use among all HRT users. Analysis of the pooled data from the WHI intervention and extended postintervention follow-up of two hormone therapy trials did not find any statistically significant results for the incidence or mortality from colorectal cancer (Manson et al., 2017). For CEE alone versus placebo, HR = 1.21 and 95% CI, 0.79-1.84 and for CEE plus MPA versus placebo, HR = 1.44 and 95% confidence interval, 0.97-2.15. Although in many cases, HRT has positive impact on the incidence of colorectal cancer and mortality, the precise mechanism by which estrogen or progesterone reduces the risk of colon cancer is not exactly known. It is believed that HRT decreases pancreatic bile acids that may responsible to promote colon cancer incidence in women (Burkman et al., 2001). Regardless of the underlying mechanism by which HRT protects against colorectal cancer, health professionals should consider its benefit when prescribing HRT to women.

2.3.9 Diabetes

Diabetes mellitus is a chronic metabolic disorder that is primarily associated with the imbalance of glucose and insulin levels in the bloodstream. Based on the nature of the diabetes, it is classified as Type 1 and Type 2. Around 10% of the cases are Type 1 and 90% are Type 2. According to the International Diabetic Federation (IDF), there are

about 371 million people worldwide who have diabetes. In recent years, the number of people diagnosed with diabetes in the UK is estimated to be 3.5 million and among them 44% are women (Diabetes, 2015). This represents 1 in every 16 women having diabetes in the UK. However, little is known about the effect of hormone replacement therapy on female diabetic patients. Margolis et al. (2004) examined the effect of postmenopausal hormone therapy on diabetes incidence and insulin resistance. They reanalysed WHI randomized control data on 15,641 postmenopausal women of ages 50−79 to estimate the risk and benefits of HRT in diabetic patients. Their findings suggest that combined therapy with oestrogen and progestin reduces the incidence of diabetes. The cumulative incidence of treated diabetes was 3.5% in the hormone therapy groups and 4.2% in the placebo group (HR= 0.79, 95% Cl, 0.67-0.93, P=0.004) in their result.

2.3.10 Gallbladder disease

Gallbladder disease is more common in women than men. An observational study by Uhler et al. published in 2000, concluded that estrogen increases the risk of formation of gallstones in postmenopausal women. Another observational study by Grodstein et al. (1994) conducted on 54,845 postmenopausal United States nurses suggests that current estrogen hormone therapy users may have a greater risk of cholecystectomy (RR 2.1; 95% CI 1.9−2.4) than never-users. In contrast, some studies failed to show any significant difference on the rate of gallbladder disease between the hormone user groups and the control groups (Palacios, 2002). Thus further research needed to con-

firm these results and women should be informed about the risks of the disease before prescribing HRT.

2.3.11 Headache and Migraine

Headache is a common symptom in most perimenopausal women. It is also one of the side effects of receiving HRT treatment. However, it is not a widely reported complaint. As a result, there are few data available on the association between headache and migraine, and the use of HRT. In 2000, a study conducted by Leicester menopause clinic on 1,000 HRT user found that 85% suffered recurrent headache of which 73% reported headache more than once a month and migraine was reported by 24 percent of women (Hodson et al., 2000). Some research shows that current use of HRT improves outcomes associated with headache and migraine.

2.4 Pattern and prevalence of HRT use in the UK

Each year, approximately 1.5 million women experience unpleasant menopausal symptoms in the UK (NICE, 2015). Among them around 400,000 suffer to troublesome extent. In 1965, HRT became available in the UK. The National Institute for Health and Care Excellence (NICE) estimates that just 1 women in every 10 of those going through menopause is currently prescribed HRT (NICE, 2015). The prevalence of HRT use rose from 18.6% to 27.7% among women aged 45−64 between 1992 and 1998, which was an increase of 49% (Bromley et al., 2004). The MWS reported that the prevalence of HRT use was 33%−34% each year from 1996 to 2000 in UK women

who participated in their survey. They also reported that current use of HRT was about twice common at age 50−54 than 60−64 with a little variation by time and region. The Figure 2.2 shows that this trend also matches with the Bromley et al. (2004) study. In 2000, more than 6 million women were prescribed HRT in England (The Telegraph, 2018). Following the WHI 2002 report that HRT increases the breast cancer incidence, HRT users in the UK decreased to 3.8 million by 2004. According to the national costing report of menopause published in November 2015, the baseline percentage of women aged 40−65 using HRT is 17%, and among them transdermal HRT user is 20% (NICE, 2015). In 2017, 2.3 million HRT prescriptions of different preparations were issued in the UK (The Telegraph, 2018). Recent reports from WHI and some other research revealed potential benefits of its use, and that the benefits may exceed the risks. A new review report published by the NICE forecasts that the number of HRT user could be doubled within next ten years.

2.5 NICE guidelines on HRT use

The National Institute for Health and Care Excellence (NICE) was originally set up in 1999 and it is recognised as a special health authority in England (NICE, 2018). Its main duty is to reduce variation in the quality and availability of NHS treatments and care. It also provides national guidance and advice for the improvement of health and social care. NICE has given some guidelines on the diagnosis and management of menopause, including women who have premature ovarian insufficiency. According to the NICE guideline (2015), HRT does not increase CVD risk when started in

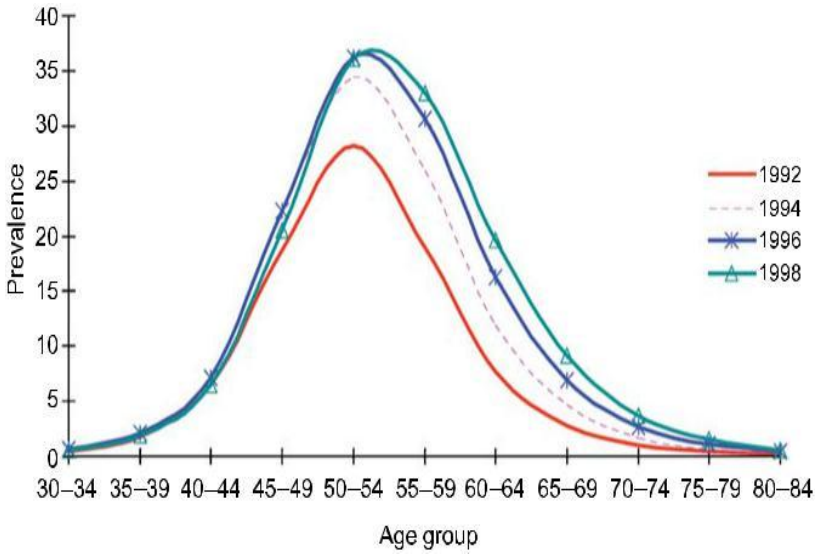

Figure 2.2: Prevalence of the use of HRT in the UK within different age group between 1992−1998. Most women used HRT at the age of 50−54 and this trend increases over the time interval. Figure extracted from Bromley et al. (2004).

women aged below 60 years and does not affect the risk of dying from cardiovascular disease. Estrogen-only HRT is associated with little or no change in the risk of breast cancer but combined HRT can be associated with an increase risk of breast cancer incidence. The effect of HRT on the risk of developing dementia is unknown. HRT should not recommended as the first treatment of choice to prevent bone loss, though it is currently valid treatment for younger postmenopausal women. Any type of HRT is not associated with an increased risk of developing type 2 diabetes. In general, HRT should not recommended for women with a history of breast cancer, endometrial cancer, stroke or deep-vein thrombosis.

2.6 Knowledge gaps

Numerous studies on the risks and benefits of HRT treatment have been undertaken from the late 80's. These studies include observational, case-controls design, meta-analyses and randomised control trials. Majority of the studies were observational as the randomised control trials are expensive and time consuming. Most studies took place in the developed countries such as Europe and America. Little is known about the HRT use in developing countries. The Nurses' health study and WHI randomised control trial in the USA, and the Million Women Study in the UK took the leading position in HRT research because of the large study populations. Based on these studies, several important results have been published regarding the use of HRT and its impact. However, each study has some limitations in terms of the study design and various factors. So rigorous investigation is required to establish the actual risks and benefits of the use of HRT. The WHI trial on HRT is recognised as one of the largest studies, but it considered only one dose and route of HRT (estrogen, 0.625 mg oral CEE and progesterone, 2.5 mg oral MPA) for all age groups in the trial. The outcomes from other doses and routes are not well known. Many experts commented that the dose was too high for older postmenopausal women. The WHI results also may not be applicable for the women in the UK since the profile of the US women in the WHI study differs from the UK women. The average age of women in the WHI study was 63.2 whereas the average age of the women in MWS was 56.7. The WHI study was based on North-American women, often overweight and frequent smokers. The average BMI of WHI participants was 28.5 kg/m^2 which is much higher than

MWS women, and this is usually a recognised risk factor of heart disease and breast cancer. Most studies on HRT examined the risks and benefits of its use, and mortality, and morbidity considering the oral routes of administration only. Less is known about the outcomes from other routes of administration.

2.7 Summary

Most women receive HRT treatment to get relief from awful climacterial symptoms. Menopause also increases the risks of developing some other medical conditions in women such as osteoporosis, dementia, cardiovascular disease, endometrial cancer and ovarian cancer. The probabilities that a menopausal woman will develop various chronic diseases over her lifetime has been estimated to be 46% for CHD, 20% for stroke, 15% for hip fracture, 10% for breast cancer, and 2.6% for endometrial cancer (Grady et al., 1992). Long-term use of HRT has been associated with reduced risk of coronary heart disease, lung cancer, dementia, and migraine. However, increased breast cancer risk has been associated with the long duration of HRT use and it is believed that the impact of estrogen on the development of breast cancer is significant. But the researchers are still not clear about how estrogen causes breast cancer. Results showed that the combined HRT decreases the breast cancer and endometrial cancer risk. Overall, results from observational studies and meta-analyses showed that HRT prevents osteoporotic fractures, CHD, gallbladder disease, diabetes, and colon cancer. Risks include breast cancer, endometrial cancer, ovarian cancer, stroke, thromboembolic events with five or more years of use. Research also found that early start of

HRT after the event of menopause and its continuation for more than five years could reduce many life-threatening diseases such as osteoporosis, cardiovascular disease and dementia. We intend to analyse the THIN primary care data to obtain further insights on the risks and benefits of HRT on general population of women in the UK.

Appendices

Appendix A

Past research on HRT

In this appendix, we tabulated research summary of various published papers on HRT that we have considered and described for the literature review. We presented the journals in chronological order. We also note down the design and setting, study period, sample size, and the statistical method used to produce the results. Finally, outcome measures and the results are summarised.

Table A.1: *Past research publications on Hormone Replacement Therapy*

Lead author (year published)	Design and setting	Study period	Sample size	Statistical method	Results
Hunt et. al (1987)	Women aged 45 – 54 were recruited at 21 specialist menopause clinic around Britain to monitor mortality and cancer incidence. Past medical history, height, weight, blood pressure, marital status, occupations and smoking with a detailed HRT history was documented at the start of the study.	1974 – 1983	4,544	Logistic regression	Overall mortality was significantly lower than the national mortality rates (Relative Risk (RR) =0.58; 95% Confidence Interval (CI), 0.49-0.70) among HRT user apart from the ovarian cancer (RR=1.43; 95% Cl, 0.62 – 2.82).
Colditz et al. (1987)	US women of aged 30 – 55 years were recruited to determine the link of HRT on CHD	1976 – 1982	121,700	Proportional hazard model	Bilateral oophorectomy increases the risk of CHD
Stampfer et al. (1991)	A cohort of female registered nurse in the US completed a set of mailed questionnaire about estrogen use and followed up for 10 years with two years periodic resurvey Prior history of cardiovascular disease and cancer were excluded at baseline	1976-1986	48, 470	Proportional hazard model	Current estrogen use was associated with a reduction in the incidence of CHD as well as mortality from CVD, but it was not associated with any change in the risk of stroke. The overall RR of CHD in women currently taking estrogen was 0.56 and 95% CI, 0.40 – 0.80.

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Table A.1 – *Continued from previous page*

Lead author (year published)	Design and setting	Study period	Sample size	Statistical method	Results
Paganini-Hill and Henderson (1994)	A prospective cohort study of residents of Leisure World Laguna Hills, a retirement community in Southern California was conducted by mailed questionnaires to evaluate the estrogen deficiency and risk of AD in women.	1981 – 1993	8,877 (3760 died)	Univariate and multivariate regression techniques	The risk of Alzheimer's disease and related dementia was less in estrogen users relative to nonusers (odds ratios (OR)= 0.69, 95% CI, 0.46 – 1.03). The risk decreased significantly with increasing estrogen dose and with increasing duration of estrogen use.
Folsom et al. (1995)	The Iowa Women's Health Study was performed by mailed questionnaires.	1986 – 1991	41,070	Proportional hazards regression model	The multivariate adjusted relative risk of current hormone user compared to non-users are: total mortality (RR = 0.78, 95% CI, 0.65 – 0.94), CHD (RR = 0.74, 95% CI, 0.48 – 1.12), endometrial cancer (RR = 4.3, 95% CI, 2.7 – 6.9), breast cancer (RR = 1.23, 95% CI, 0.99 – 1.55), colon cancer (RR = 0.72, 95% CI, 0.46 – 1.12), hip fracture (RR = 0.53, 95% CI, 0.31 – 0.91).
Paganini-Hill and Henderson (1996)	A prospective cohort study of residents of Leisure World Laguna	1981 – 1995	8,877 (3760 died)	Proportional hazards model	The risk of AD and related dementia was significantly reduced in estrogen user compared with non-users (OR =

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Table A.1 – *Continued from previous page*

Lead author (year published)	Design and setting	Study period	Sample size	Statistical method	Results
	Hills, was conducted by mailed questionnaires to evaluate the effects of different estrogen preparation, varying doses of estrogen, and duration of estrogen replacement therapy on the risk of developing AD				0.65, 95% CI, 0.49 – 0.88). The risk decreased significantly with both increasing doses ($P = 0.01$) and and increasing duration ($P = 0.01$) in women taking oral CEE.
Ettinger et al. (1996)	Cohort women born between 1900 and 1915 were selected to compare all-cause and cause-specific mortality rates on long-term use of ERT	1969-1973	1,110	Cox-proportional hazards model	For death from any cause, the age-adjusted RR = 0.54 and associated 95% CI= 0.38 – 0.76 in estrogen users compared to non-user.
Kawas et al. (1997)	A prospective study of ERT and the risk of developing Alzheimers disease in the Baltimore Longitudinal Study of Aging categorized women into oral and transdermal ERT user.	16 years of follow-up	472	Cox-proportional hazards model	The RR for AD in ERT users compared to nonusers was 0.46 (95% CI, 0.209 – 0.997) after adjusting for education.
Grodstein et al. (1997)	The Nurses Health Study, where female registered USA nurses of aged 30 – 55	1976 – 1992	121,700	Logistic regression	Current hormone users had a lower risk of death (RR = 0.63, 95% CI = 0.56 – 0.70) than lifetime non-users.

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Table A.1 – *Continued from previous page*

Lead author (year published)	Design and setting	Study period	Sample size	Statistical method	Results
	completed a set of mailed questionnaires including information on menopause, CVD, and cancer.				Survival benefit decreases with longer duration (> 10) of use.
Sourander et al. (1998)	Women born between 1923 and 1930 in Turku, Finland, were invited to participate a mammography screening with questionnaires including the use of hormone therapy.	1987 – 1995 up	7,944 women contributed to 53,305 person-years follow-	Proportional hazards model	Current ERT did not increase the riskof breast cancer (HR = 0.57, 95% Cl, 0.27 – 1.20) compared to non-user.
Baldereschi et al. (1998)	The Italian Longitudinal Study of aging, a population based, multicentre survey examined the association ERT and Alzheimers disease in the postmenopausal women of age 65 – 84 years.	Not known	2,816	Proportional hazards model	ERT is associated with a reduced prevalence of AD (OR = 0.28, 95% CI, 0.08 – 0.98) after adjusting for age, education, age at menarche, age at menopause, smoking and alcohol habits, body weight at the age of 50 years, and the number of children.
Mulnard et al. (2000)	A randomized, double-blind, placebo control clinical trial to examine ERT on treatment of mild	1995 – 1999	120 women with mild	Linear and logistic regression	ERT did not show disease progression nor did it improve global, cognitive, or functional outcome in women with mild to

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Table A.1 – *Continued from previous page*

Lead author (year published)	Design and setting	Study period	Sample size	Statistical method	Results
	to moderate AD.		to moderate AD	model	moderate AD.
Hedblad et al. (2002)	An urban cohort of peri/postmenopausal women of median age 55.4 in Sweden was followed up for nine years.	1983 – 1992	5,721	Kaplan-Meier	Women affirming use of HRT had a lower incidence of myocardial infraction (MI).
Zandi et al. (2002)	Cohort study of residents of a California retirement community was performed by a postal health survey including details on ET use.	1995 –2000	1,889	Logistic model	Older women undergoing estrogen therapy treatment were significantly related to increased longevity (RR = 0.91; 95% CI, 0.87 – 0.96). There were least risk among long-term ($\geq$ 15 years) users (RR = 0.83; 95% CI, 0.74 – 0.93 for 15 – 19 years) and (RR = 0.87; 95% CI, 0.80 – 0.94 for 20+ years). Lower dose users ($\leq$ 0.625 mg) had a slightly better survival rate than higher dose user (RR = 0.84; 95% CI, 0.78 – 0.91 vs RR = 0.91; 95% CI, 0.83 – 0.97).
Lacey et al. (2002)	A cohort study of former participants in the Breast Cancer Detection Demonstration Project, a nationwide breast cancer	1979 – 1998	44,241	Poisson regression model	Incident of ovarian cancer was the main outcome measure. 329 women developed ovarian cancer during follow-up. Time dependent analysis adjusted for age, menopause type,

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Table A.1 – *Continued from previous page*

Lead author (year published)	Design and setting	Study period	Sample size	Statistical method	Results
	screening programme at twenty-nine US clinical centres. The average age of women was 56.6 years				oral contraceptive use, ever use of estrogen-only was significantly associated with ovarian cancer (RR = 1.6; 95% Cl, 1.2 – 2.0). Increasing duration of estrogen-only use was significantly associated with ovarian cancer.
Hodiset al. (2003)	A double blinded, placebo control trial on women mean age 63.5 and had at least one coronary-artery lesion. Participants were randomly assigned to either control group, estrogen-only (17β - estradiol), or estrogen-progestin group (17β - estradiol and medroxyprogesterone acetate)	1995 – 2000	226	ANOVA and chi-square test	In older postmenopausal women with established coronary-artherosclerosis, estrogen-onlyorestrogen-progestin therapy had no significant effect on the progression of atherosclerosis.
Beral et al. (2003)	A breast screening programme conducted by The National Health Service (NHS) invites all women in the UK of aged 50 – 64 years for routine screening together with	1996 – 2001	1,084,110 person-year follow-up	Cox's regression model	Half of the participant women had used HRT. Among them 9364 incident of breast cancers and 637 breast cancer deaths were registered after an average of 2.6 and 4.1 years of follow-up, respectively. Women using HRT at recruitment were more likely to

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Table A.1 – *Continued from previous page*

Lead author (year published)	Design and setting	Study period	Sample size	Statistical method	Results
	some postal questionnaire about use of HRT. The questionnaire is returned before women are screened.				develop breast cancer than never user (RR = 1.66; 95% CI, 1.58 – 1.75, $P < 0.0001$) and die from it (RR =; 1.22; 95% CI, 1.00 – 1.48, $P = 0.05$). The risk was significantly increased for women receiving HRT preparation containing oestrogen-progestogen (RR = 2.00; 95% CI, 1.88 – 2.12, $P < 0.0001$).
Margolis et al. (2004)	A randomised, double-blinded Women's Health Initiative trial on postmenopausal women of age 50 to 79 with intact uterus were used to examine the incidence of diabetes among HRT user.	1993 – 2001	15,641	Cox's regression model	Study suggest that combined therapy reduces the incidence of diabetes, possibly mediated by a decrease in insulin resistance unrelated to body size. The cumulative incidence of treated diabetes was 3.5% in the hormone therapy groups and 4.2% in the placebo group (HR = 0.79, 95% Cl, 0.67 – 0.93, $P = 0.004$)
Paganini-Hill et al. (2006)	Cohort study of residents of a California retirement community was performed by a postal health survey including details on ET use.	1981 – 2003	122,203 person-years follow-up	Cox's regression model	Older women undergoing estrogen therapy treatment were significantly related to increased longevity (RR = 0.91; 95% CI, 0.87 – 0.96). There were least risk among long-term ($\geq$ 15 years) users (RR = 0.83; 95% CI, 0.74 – 0.93 for 15 – 19 years) and (RR = 0.87; 95% CI, 0.80 – 0.94 for 20+ years). Lower

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Table A.1 – *Continued from previous page*

Lead author (year published)	Design and setting	Study period	Sample size	Statistical method	Results
					dose users (0.625 mg) had a slightly better survival rate than higher dose user (RR = 0.84; 95% CI, 0.78 – 0.91 vs RR = 0.91; 95% CI, 0.83 – 0.97).
Schuetz et al. (2007)	This is a single centre analysis in the Breast Unit of the Department of Gynecology and Obstetrics at the University Hospital of Heidelberg. The inclusion criteria were the primary patients with breast cancer aged 45-70 years. Among them who received HRT for less than 12 months were included in the never user groups.	1990 – 1999	1,072	Cox regression model Kaplan-Meier graph	The use of HRT before the diagnosis of breast cancer results in more favourable primary tumours, with a lower incidence of recurrences and a better overall survival rate. 5-year survival was 92% (Hazard ratio, 0.37; 95% Cl, 0.24 – 0.57)
MacGregoret al. (2007)	A meta-analysis of MEDLINE search reviews considered the effects of menopause and hormone replacement therapy (HRT) on headache and migraine	1950 – 2007	1,436	Hierarchical Bayesian random-effects model	There is an increased longevity in younger postmenopausal women taking hormone therapy compared to those who are not taking the therapy.
Gast et al.	Data from a Dutch and	1997 – 2007	91,310	Cos	After multivariate adjustment, ever HT

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Table A.1 – *Continued from previous page*

Lead author (year published)	Design and setting	Study period	Sample size	Statistical method	Results
(2011)	Swedish women of age 46 – 64 years who are free from coronary heart disease (CHD), stroke, venous thrombosis/ pulmonary embolism or cancer at baseline were considered. Information on hormone therapy, vasomotor symptoms (VMS) and potential confounder were collected by questionnaires		pearson-years	regression model	user was not associated with the risk of CHD compared with non-user among women with or without intense VMS.
Hunter et al. (2011)	Cross-sectional study contributed by the UK collaborative trial of Ovarian Cancer Screening (UKCTOCS) cohort. Women without oophorectomy and aged of 54 – 65 years completed a follow-up questionnaire.	2001 – 2008	10,418	Binary logistic regression	Women who had taken HT in the past and discontinued the treatment were more likely to havehot flashes and night sweat.
Schierbeck et al. (2012)	Randomised, open label trial of healthy Danish	1990 – 1993	2,016	Proportional hazards	Early initiation and prolonged HRT significantly reduces the risk of the

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Table A.1 – *Continued from previous page*

Lead author (year published)	Design and setting	Study period	Sample size	Statistical method	Results
	women aged between 45 – 58 were performed and followed up to death, cardiovascular disease, and cancer.			model	combined endpoint of mortality, myocardial infraction or heart failure and did not result in an increased risk of breast cancer or stroke.
Anderson et al. (2012)	Hysterectomised women of aged 50-79 years were selected from the WHI randomised, double-masked, placebo-controlled trial at 40 US clinical centres to examine the effect of oestrogen (0.625 mg) on invasive breast cancer incidence, tumour characteristics, and mortality.	1993 – 1998	10,739	Cox's regression model	The use of oestrogen was associated with lower incidence of invasive breast cancer (151 cases, 0.27% per year) compared with placebo (199 cases, 0.35% per year); (HR 0.77, 95% CI 0.62 – 0.95: $P = 0.02$) after a median of 5.9 years of follow-up.
Manson et al. (2013)	TwoWHI hormone therapy trial (CEE alone vs. placebo and CEE plus MPA vs. placebo) were used to find out the health outcome in Intervention and Extended poststopping	1993 – 1998	27,347	Cox's regression model	The number of CHD cases were 196 for CEE plus MPA vs 159 for placebo (HR = 1.18, 95% CI, 0.95 – 1.45), and 206 vs 155 for invasive breast cancer (HR = 1.24, 95% CI, 1.01 – 1.53).For CEE alone, younger women (aged 50 – 59) had more favourable results for all-cause of mortality, myocardial infraction,

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Table A.1 – *Continued from previous page*

Lead author (year published)	Design and setting	Study period	Sample size	Statistical method	Results
	Phases.Intervention lasted a median of 5.6 years in CEE plus MPA trial and 7.2 years in CEE trial with 13 years of cumulative follow-up until September 30, 2010.				and the global index.
Boardman et al. (2015)	A meta-analysis of 19 RCTs to assess the effects of oral HT for the prevention of cardiovascular disease in postmenopausal women, and whether there are differential effects between use in primary or secondary prevention	Not known	40,410		Results shows no evidence that hormone therapy provides any protective effects against death from any cause, death from cardiovascular disease, non-fatal heart attack or angina, either in healthy women or women with pre-existing heart disease.
Imtiaz et al. (2017)	A large prospective study from the Kuopio Osteoporosis Risk Factor and Prevention study cohort in Finland were used to explore the association between postmenopausal HT and AD. Self-administered	1989 – 2009	8,195	Cox hazards model	Postmenopausal estrogen use was not associated with the risk of AD in register-based or self-reported data (HR = 0.92, 95% CI, 0.68 - 1.2, and HR = 0.99, 95% CI, 0.75 - 1.3, respectively). Long-term self-reported postmenopausal HT was associated with reduced AD risk (HR = 0.53, 95% CI, 0.31 - 0.91).

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Table A.1 – *Continued from previous page*

Lead author (year published)	Design and setting	Study period	Sample size	Statistical method	Results
	questionnaires were sent to all women aged 47 - 56 years in every 5th year, starting from 1989. Register-based information on HT prescriptions was available since 1995.				
Manson et al. (2017)	WHI trial on postmenopausal women of age 50 to 79 were used to examine the total and cause specific cumulative mortality, including during the intervention and extended postintervention follow-up up to December 31, 2014	1993 – 1998	27,347 (7,489 died)	Cox hazards model	During the cumulative 18 years follow-up, all-cause mortality was 27.1% in the hormone therapy group and vs 27.6% in the placebo group (HR = 0.99, 95% CI, 0.94 – 1.03). Hormone therapy with CEE plus MPA for a median of 5.6 years or with CEE alone for a median of 7.2 years was not associated with risk of all-cause, cardiovascular, or cancer mortality.

Bibliography

Adami, H.-O., Persson, I., Hoover, R., Schairer, C., and Bergkvist, L. (1989). Risk of cancer in women receiving hormone replacement therapy. *International journal of cancer*, 44(5):833–839.

Alzheimer's Associations, title = About dementia, y. . . h. . https://www.alz.org/what-is-dementia.asp. n. . A.

Anderson, G., Cummings, S., Freedman, L., Furberg, C., Henderson, M., Johnson, S., Kuller, L., Manson, J., Oberman, A., Prentice, R., et al. (1998). Design of the women's health initiative clinical trial and observational study. *Controlled clinical trials*, 19(1):61–109.

Anderson, G. L., Autier, P., Beral, V., Bosland, M. C., Fernández, E., Haslam, S. Z., Kaufman, D. G., La Vecchia, C., Molinolo, A. A., Newcomb, P. A., et al. (2007). Combined estrogen-progestogen menopausal therapy. In *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans*.

Baldereschi, M., Di Carlo, A., Lepore, V., Bracco, L., Maggi, S., Grigoletto, F., Scarlato, G., Amaducci, L., et al. (1998). Estrogen-replacement therapy and alzheimer's disease in the italian longitudinal study on aging. *Neurology*, 50(4):996–1002.

Boardman, H. M., Hartley, L., Eisinga, A., Main, C., Roqué i Figuls, M., Bonfill Cosp, X., Gabriel Sanchez, R., and Knight, B. (2015). Hormone therapy for preventing cardiovascular disease in post-menopausal women. *The Cochrane Library*.

Brenner, D. E., Kukull, W. A., Stergachis, A., Van Belle, G., Bowen, J. D., McCormick, W. C., Ten, L., and Larson, E. B. (1994). Postmenopausal estrogen replacement therapy and the risk of alzheimer's disease: a population-based case-control study. *American Journal of Epidemiology*, 140(3):262–267.

British Heart Foundation (July, 2016). CVD Statistics. https://www.bhf.org.uk/-/media/files/.../heart.../bhf-cvd-statistics---uk-factsheet.pdf. Accessed: 2018-01-12.

Bromley, S., Vries, C., and Farmer, R. (2004). Utilisation of hormone replacement therapy in the united kingdom. *BJOG: An International Journal of Obstetrics & Gynaecology*, 111(4):369–376.

Bupa (2018). Menopause. https://www.bupa.co.uk/health-information/directory/m/menopause. Accessed: 2018-03-06.

Burkman, R. T., Collins, J. A., and Greene, R. A. (2001). Current perspectives on benefits and risks of hormone replacement therapy. *American Journal of Obstetrics & Gynecology*, 185(2):S13–S23.

Calle, E. E., Miracle-McMahill, H. L., Thun, M. J., and Heath Jr, C. W. (1995). Estrogen replacement therapy and risk of fatal colon cancer in a prospective cohort of postmenopausal women. *JNCI: Journal of the National Cancer Institute*, 87(7):517–523.

Cancer Research UK (July, 2015). Bowel Cancer Statistics. http://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/bowel-cancer#heading-One. Accessed: 2018-03-19.

Cass, I. and Runowicz, C. (1998). Menopause and controversies in hormone replacement therapy. *AMERICAN JOURNAL OF MANAGED CARE*, 4(2):257–262.

Cauley, J. A., Robbins, J., Chen, Z., Cummings, S. R., Jackson, R. D., LaCroix, A. Z., LeBoff, M., Lewis, C. E., McGowan, J., Neuner, J., et al. (2003). Effects of estrogen plus progestin on risk of fracture and bone mineral density: the women's health initiative randomized trial. *Jama*, 290(13):1729–1738.

Christiansen, C. (1996). Hormone replacement therapy and osteoporosis. *Maturitas*, 23:S71–S76.

Cirigliano, M. (2007). Bioidentical hormone therapy: a review of the evidence. *Journal of Women's Health*, 16(5):600–631.

Cokkinides, V., Albano, J., Samuels, A., Ward, M., and Thum, J. (2005). American cancer society: Cancer facts and figures. *Atlanta: American Cancer Society*.

Diabetes, U. (2015). Facts and stats. diabetes uk, london.

Emily et al., v. (2003). Breast cancer and hormone-replacement therapy in the million women study. *The Lancet*, 362(9382):419–427.

Ettinger, B., Friedman, G. D., Bush, T., and Quesenberry Jr, C. P. (1996). Reduced mortality associated with long-term postmenopausal estrogen therapy. *Obstetrics & Gynecology*, 87(1):6–12.

FDA (July, 2018). Menopause Hormone Therapy. https://www.fda.gov/ForConsumers/ByAudience/ForWomen/ucm118627.htm. Accessed: 2018-03-03.

Folsom, A. R., Anderson, J. P., and Ross, J. A. (2004). Estrogen replacement therapy and ovarian cancer. *Epidemiology*, 15(1):100–104.

Folsom, A. R., Mink, P. J., Sellers, T. A., Hong, C.-P., Zheng, W., and Potter, J. D. (1995). Hormonal replacement therapy and morbidity and mortality in a prospective study of postmenopausal women. *American Journal of Public Health*, 85(8_Pt_1):1128–1132.

Freeman, E. and Sherif, K. (2007). Prevalence of hot flushes and night sweats around the world: a systematic review. *Climacteric*, 10(3):197–214.

Galaal, K., Al Moundhri, M., Bryant, A., Lopes, A. D., and Lawrie, T. A. (2014). Adjuvant chemotherapy for advanced endometrial cancer. *The Cochrane Library*.

Gast, G.-C. M., Pop, V. J., Samsioe, G. N., Grobbee, D. E., Nilsson, P. M., Keyzer, J. J., Wijnands-van Gent, C. J., and van der Schouw, Y. T. (2011a). Hormone therapy and coronary heart disease risk by vasomotor menopausal symptoms. *Maturitas*, 70(4):373–378.

Gast, G.-C. M., Pop, V. J., Samsioe, G. N., Grobbee, D. E., Nilsson, P. M., Keyzer, J. J., Wijnands-van Gent, C. J., and van der Schouw, Y. T. (2011b). Vasomotor menopausal symptoms are associated with increased risk of coronary heart disease. *Menopause*, 18(2):146–151.

Gauthier, A., Kanis, J. A., Jiang, Y., Martin, M., Compston, J. E., Borgström, F., Cooper, C., and McCloskey, E. V. (2011). Epidemiological burden of postmenopausal osteoporosis in the uk from 2010 to 2021: estimations from a disease model. *Archives of osteoporosis*, 6(1-2):179–188.

GP Notebook (2016). Menopause. https://www.gpnotebook.co.uk/simplepage.cfm?ID=1288699910. Accessed: 2018-02-12.

Grady, D., Gebretsadik, T., Kerlikowske, K., Ernster, V., and Petitti, D. (1995). 95039031 hormone replacement therapy and endometrial cancer risk: A meta-analysis. *Maturitas*, 22(3):265.

Grady, D., Rubin, S. M., Petitti, D. B., Fox, C. S., Black, D., Ettinger, B., Ernster, V. L., and Cummings, S. R. (1992). Hormone therapy to prevent disease and prolong life in postmenopausal women. *Annals of internal medicine*, 117(12):1016–1037.

Grodstein, F., Colditz, G. A., and Stampfer, M. J. (1994). Postmenopausal hormone use and cholecystectomy in a large prospective study. *Obstetrics & Gynecology*, 83(1):5–11.

Grodstein, F., Newcomb, P. A., and Stampfer, M. J. (1999). Postmenopausal hormone therapy and the risk of colorectal cancer: a review and meta-analysis. *The American journal of medicine*, 106(5):574–582.

Grodstein, F. and Stampfer, M. (1995). The epidemiology of coronary heart disease and estrogen replacement in postmenopausal women. *Progress in cardiovascular diseases*, 38(3):199–210.

Grodstein, F., Stampfer, M. J., Colditz, G. A., Willett, W. C., Manson, J. E., Joffe, M., Rosner, B., Fuchs, C., Hankinson, S. E., Hunter, D. J., et al. (1997). Postmenopausal hormone therapy and mortality. *New England Journal of Medicine*, 336(25):1769–1776.

Hampton, T. (2009). Lung cancer mortality higher in women who used combination hormone therapy. *Jama*, 302(6):615–616.

Harris, R., Whittemore, A. S., Itnyre, J., and Group, C. O. C. (1992). Characteristics relating to ovarian cancer risk: collaborative analysis of 12 us case-control studies:

Iii. epithelial tumors of low malignant potential in white women. *American Journal of Epidemiology*, 136(10):1204–1211.

Harvard School of Public Health. Nurses Health Studies. https://www.hsph.harvard.edu/nutritionsource/nurses-health-study/. Accessed: 2018-03-21.

Healthline (2018). Physical Exam. https://www.healthline.com/health/menopause/tests-diagnosis. Accessed: 2018-03-06.

Henderson, V. W. (2014). Alzheimer's disease: review of hormone therapy trials and implications for treatment and prevention after menopause. *The Journal of steroid biochemistry and molecular biology*, 142:99–106.

Henderson, V. W., Paganini-Hill, A., Emanuel, C. K., Dunn, M. E., and Buckwalter, J. G. (1994). Estrogen replacement therapy in older women: comparisons between alzheimer's disease cases and nondemented control subjects. *Archives of Neurology*, 51(9):896–900.

Hodis, H. N. and Mack, W. J. (2014). Hormone replacement therapy and the association with coronary heart disease and overall mortality: clinical application of the timing hypothesis. *The Journal of steroid biochemistry and molecular biology*, 142:68–75.

Hodis, H. N., Mack, W. J., Azen, S. P., Lobo, R. A., Shoupe, D., Mahrer, P. R., Faxon, D. P., Cashin-Hemphill, L., Sanmarco, M. E., French, W. J., et al. (2003). Hormone therapy and the progression of coronary-artery atherosclerosis in postmenopausal women. *New England Journal of Medicine*, 349(6):535–545.

Hodson, J., Thompson, J., and Al-Azzawi, F. (2000). Headache at menopause and in hormone replacement therapy users. *Climacteric*, 3(2):119–124.

Hulley, S., Grady, D., Bush, T., Furberg, C., Herrington, D., Riggs, B., Vittinghoff, E., Heart, Group, E. R. S. H. R., et al. (1998). Randomized trial of estrogen plus progestin for secondary prevention of coronary heart disease in postmenopausal women. *Jama*, 280(7):605–613.

Hunt, K., Vessey, M., and McPHERSON, K. (1990). Mortality in a cohort of long-term users of hormone replacement therapy: an updated analysis. *BJOG: An International Journal of Obstetrics & Gynaecology*, 97(12):1080–1086.

ILCUK (2010). Osteoporosis in the UK. http://www.ilcuk.org.uk/index.php/publications/publication_details/osteoporosis_in_the_uk_at_breaking_point. Accessed: 2018-03-06.

Imtiaz, B., Tuppurainen, M., Rikkonen, T., Kivipelto, M., Soininen, H., Kröger, H., and Tolppanen, A.-M. (2017). Postmenopausal hormone therapy and alzheimer disease a prospective cohort study. *Neurology*, 88(11):1062–1068.

Kawas, C., Resnick, S., Morrison, A., Brookmeyer, R., Corrada, M., Zonderman, A., Bacal, C., Lingle, D. D., and Metter, E. (1997). A prospective study of estrogen replacement therapy and the risk of developing alzheimer's disease the baltimore longitudinal study of aging. *Neurology*, 48(6):1517–1521.

Lacey Jr, J. V., Mink, P. J., Lubin, J. H., Sherman, M. E., Troisi, R., Hartge, P., Schatzkin, A., and Schairer, C. (2002). Menopausal hormone replacement therapy and risk of ovarian cancer. *Jama*, 288(3):334–341.

LeBlanc, E. S., Janowsky, J., Chan, B. K., and Nelson, H. D. (2001). Hormone replacement therapy and cognition: systematic review and meta-analysis. *Jama*, 285(11):1489–1499.

Manson, J. E., Aragaki, A. K., Rossouw, J. E., Anderson, G. L., Prentice, R. L., LaCroix, A. Z., Chlebowski, R. T., Howard, B. V., Thomson, C. A., Margolis, K. L., et al. (2017). Menopausal hormone therapy and long-term all-cause and cause-specific mortality: the womens health initiative randomized trials. *Jama*, 318(10):927–938.

Manson, J. E., Chlebowski, R. T., Stefanick, M. L., Aragaki, A. K., Rossouw, J. E., Prentice, R. L., Anderson, G., Howard, B. V., Thomson, C. A., LaCroix, A. Z., et al. (2013). Menopausal hormone therapy and health outcomes during the intervention and extended poststopping phases of the womens health initiative randomized trials. *Jama*, 310(13):1353–1368.

Manson, J. E. and Martin, K. A. (2001). Postmenopausal hormone-replacement therapy. *New England Journal of Medicine*, 345(1):34–40.

Margolis, K., Bonds, D., Rodabough, R., Tinker, L., Phillips, L., Allen, C., Bassford, T., Burke, G., Torrens, J., Howard, B., et al. (2004). Effect of oestrogen plus

progestin on the incidence of diabetes in postmenopausal women: results from the womens health initiative hormone trial. *Diabetologia*, 47(7):1175–1187.

Mayo Clinic (2018). Menopause: Diagnosis and Treatment. https://www.mayoclinic.org/diseases-conditions/menopause/diagnosis-treatment/drc-20353401. Accessed: 2018-02-12.

McGuire, S. (2016). World cancer report 2014. geneva, switzerland: World health organization, international agency for research on cancer, who press, 2015. *Advances in Nutrition: An International Review Journal*, 7(2):418–419.

Mulnard, R. A., Cotman, C. W., Kawas, C., van Dyck, C. H., Sano, M., Doody, R., Koss, E., Pfeiffer, E., Jin, S., Gamst, A., et al. (2000). Estrogen replacement therapy for treatment of mild to moderate alzheimer disease: a randomized controlled trial. *Jama*, 283(8):1007–1015.

NHS Choices (July, 2015). Lung cancer in women. https://www.nhs.uk/Livewell/Lungcancer/Pages/Womenandlungcancer.aspx. Accessed: 2018-01-12.

NHS Choices (July, 2016). HRT hormones. https://www.nhs.uk/conditions/hormone-replacement-therapy-hrt/types/. Accessed: 2018-01-12.

NICE (2015). Putting NICE guidence into practice. https://www.nice.org.uk/guidance/ng23/resources/costing-report-pdf-556376653. Accessed: 2018-03-06.

NICE (2018). Who we are. https://www.nice.org.uk/about/who-we-are. Accessed: 2018-04-25.

Paganini-Hill, A. and Henderson, V. W. (1994). Estrogen deficiency and risk of alzheimer's disease in women. *American journal of epidemiology*, 140(3):256–261.

Paganini-Hill, A. and Henderson, V. W. (1996). Estrogen replacement therapy and risk of alzheimer disease. *Archives of internal medicine*, 156(19):2213–2217.

Palacios, S. (2002). Long-term hormone replacement therapy use is no longer controversial. In *International Congress Series*, volume 1229, pages 127–131. Elsevier.

Panay, N., Hamoda, H., Arya, R., and Savvas, M. (2013). The 2013 british menopause society & womens health concern recommendations on hormone replacement therapy. *Menopause international*, 19(2):59–68.

Persson, I., Weiderpass, E., Bergkvist, L., Bergström, R., and Schairer, C. (1999). Risks of breast and endometrial cancer after estrogen and estrogen–progestin replacement. *Cancer Causes & Control*, 10(4):253–260.

Persson, I., Yuen, J., Bergkvist, L., and Schairer, C. (1996). Cancer incidence and mortality in women receiving estrogen and estrogen-progestin replacement therapylong-term follow-up of a swedish cohort. *International journal of cancer*, 67(3):327–332.

Rossouw et al., G. (2002). Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the women's health initiative randomized controlled trial. *Jama*, 288(3):321–333.

Salpeter, S. R., Cheng, J., Thabane, L., Buckley, N. S., and Salpeter, E. E. (2009). Bayesian meta-analysis of hormone therapy and mortality in younger postmenopausal women. *The American journal of medicine*, 122(11):1016–1022.

Salpeter, S. R., Walsh, J. M., Greyber, E., Ormiston, T. M., and Salpeter, E. E. (2004). Mortality associated with hormone replacement therapy in younger and older women. *Journal of general internal medicine*, 19(7):791–804.

Schierbeck, L. L., Rejnmark, L., Tofteng, C. L., Stilgren, L., Eiken, P., Mosekilde, L., Køber, L., and Jensen, J.-E. B. (2012). Effect of hormone replacement therapy on cardiovascular events in recently postmenopausal women: randomised trial. *Bmj*, 345:e6409.

Schuetz, F., Diel, I. J., Pueschel, M., von Holst, T., Solomayer, E. F., Lange, S., Sinn, P., Bastert, G., and Sohn, C. (2007). Reduced incidence of distant metastases and lower mortality in 1072 patients with breast cancer with a history of hormone replacement therapy. *American Journal of Obstetrics & Gynecology*, 196(4):342–e1.

Shumaker, S. A., Legault, C., Kuller, L., Rapp, S. R., Thal, L., Lane, D. S., Fillit, H., Stefanick, M. L., Hendrix, S. L., Lewis, C. E., et al. (2004). Conjugated equine estrogens and incidence of probable dementia and mild cognitive impairment in postmenopausal women: Women's health initiative memory study. *Jama*, 291(24):2947–2958.

Shumaker, S. A., Legault, C., Rapp, S. R., Thal, L., Wallace, R. B., Ockene, J. K., Hendrix, S. L., Jones III, B. N., Assaf, A. R., Jackson, R. D., et al. (2003). Estrogen

plus progestin and the incidence of dementia and mild cognitive impairment in postmenopausal women: the women's health initiative memory study: a randomized controlled trial. *Jama*, 289(20):2651–2662.

Stefanick, M. L., Anderson, G. L., Margolis, K. L., Hendrix, S. L., Rodabough, R. J., Paskett, E. D., Lane, D. S., Hubbell, F. A., Assaf, A. R., Sarto, G. E., et al. (2006). Effects of conjugated equine estrogens on breast cancer and mammography screening in postmenopausal women with hysterectomy. *Jama*, 295(14):1647–1657.

The Telegraph (April, 2018). New NHS advice means number of women on HRT 'could double'. https://www.telegraph.co.uk/news/health/news/11989679/New-NHS-advice-means-number-of-women-on-HRT-could-double.html. Accessed: 2018-04-13.

Uhler, M. L., Marks, J. W., and Judd, H. L. (2000). Estrogen replacement therapy and gallbladder disease in postmenopausal women. *Menopause*, 7(3):162–167.

University of Oxford. The Million Women Study. http://www.millionwomenstudy.org/introduction/. Accessed: 2018-03-21.

Verywellhealth, title = Lung Cancer in Women, y. . . h. . https://www.verywell.com/symptoms-of-lung-cancer-in-women-2249393. n. . A.

Wang, P., Liao, S., Liu, R., Liu, C., Chao, H., Lu, S., Yu, H., Wang, S., and Liu, H.-C. (2000). Effects of estrogen on cognition, mood, and cerebral blood flow in ad a controlled study. *Neurology*, 54(11):2061–2066.

Wells, G. and Herrington, D. M. (1999). The heart and estrogen/progestin replacement study. *Drugs & aging*, 15(6):419–422.

WHI Organization. Welcome to the Women's Health Initiative. https://www.whi.org/SitePages/WHI%20Home.aspx. Accessed: 2018-03-10.

WHO (2014). *Global status report on alcohol and health, 2014*. World Health Organisation.

Women's Health Concern (November, 2017). HRT: The history. https://www.womens-health-concern.org/help-and-advice/factsheets/hrt-the-history/. Accessed: 2018-01-12.

Yao, Y., Gu, X., Zhu, J., Yuan, D., and Song, Y. (2013). Hormone replacement therapy in females can decrease the risk of lung cancer: a meta-analysis. *PLoS One*, 8(8):e71236.

Zandi, P. P., Carlson, M. C., Plassman, B. L., Welsh-Bohmer, K. A., Mayer, L. S., Steffens, D. C., Breitner, J. C., Investigators, C. C. M. S., et al. (2002). Hormone replacement therapy and incidence of alzheimer disease in older women: the cache county study. *Jama*, 288(17):2123–2129.

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