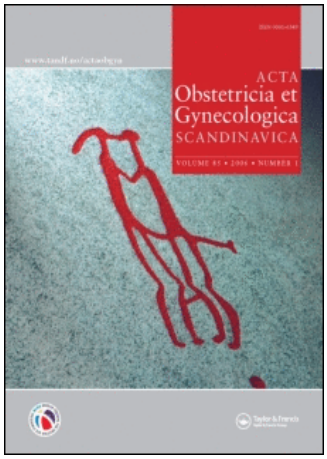

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ORIGINAL ARTICLE

Hormone replacement therapy in Denmark, 1995–2004

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Abstract

Background. Recently, the Danish National Register of Medicinal Product Statistics (NRM) was opened for research purposes, and therefore, on an individual basis, can merge with other national registers. The aim of this study was to analyse the use of hormones based on the individual data of the entire Danish female population, with the focus on a detailed evaluation of specific hormone regimens and factors associated with systemic hormone replacement therapy (HRT). *Methods*. All Danish female citizens, aged 15–70 years during the study period 1995–2004, were identified in the Civil Registration System, and their redeemed prescriptions for hormones and medication for diabetes, hypertension, hypercholesterolemia and heart conditions were retrieved from the NRM. Information on habitation, education, employment and gynaecological surgery was obtained from other national registers. *Results*. After 2002, the use of HRT was reduced by 65%. In 2002, HRT was most prevalent in women aged 55–59 years, when an average of 200 defined daily doses per 1,000 women per day was recorded. In 2002, approximately 39% of women aged 50–57 years were ever exposed to HRT. The mean duration of HRT was 5 years in an 8-year time window. During the study period, there was a significant decline in the use of systemic hormones, initially due to a decrease in cyclic combined therapy, but after 2002 continuous combined therapy decreased rapidly. HRT was positively associated with middle-term education, employment status, and living in urban areas. Women treated for diabetes used hormones less frequently than women without diabetes. Women using antiarrhythmics or antihypertensives used hormones more often than women not using this medication. HRT was positively associated with gynaecological surgery. *Conclusion*. One in five women, aged 50-59 years, redeemed daily HRT. Use of HRT declined from 1995 to 2002, but more than halved after 2002. HRT is associated to redemption of other medications of significance for health.

Key words: *Hormone Replacement Therapy, National Register of Medicinal Product Statistics, Anatomical Therapeutical Chemical, Defined daily doses, Intrauterine device, Norethisterone acetate, Cyproteroneacetate, Medroxyprogesterone acetate, Conjugated equine estrogen, Figure*

Background

In recent decades, postmenopausal systemic hormone replacement therapy (HRT) has been widely used in the western world. HRT has been prescribed primarily for climacteric symptoms, but also long-term use of HRT has been frequent as evidence from biological and observational studies suggested prevention of osteoporosis and cardiovascular disease was assumed. In 1998, the first, large scale, randomised studies with clinical end-points were published, questioning the beneficial effect of HRT on cardiovascular disease (1). Subsequently, the largest randomised studies to date also failed to confirm a beneficial effect of HRT on cardiovascular disease (2). The new scientific results have influenced the use of hormones.

HRT represents a broad spectrum of therapies with varying chemical compounds, regimens of unopposed estrogen or estrogen/progestagen combinations, routes of administration and dosages. In the observational literature, typically only few aspects of this broad spectrum of HRT has been addressed, and a randomised study has only the possibility of testing a single regimen.

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New possibilities to assess the use of medical products, such as HRT, are national registers based on individual data originally initiated to administer public refunds. In Denmark, such a register, the National Register of Medicinal Product Statistics (NRM), was established in 1994, and was recently opened for research purposes.

The aim of this study was to analyse the use of hormones based on individual data of the entire Danish female population, with the focus on a detailed description of specific HRT regimens, changes in patterns of use with time, and factors associated with HRT.

Material and methods

All female Danish citizens, aged 15–70 years during the period 1995–2004, were identified in the Civil Registration System, and their redeemed prescriptions for HRT during this period were retrieved from the NRM.

Information in the NRM is recorded under a unique identification code, after cryptating the 10 digit civil person register number. Therefore, individually based medical assessments regarding regimens and associations between HRT and other medical products are possible. Data from the NRM may be merged with other registers on an individual basis. We merged NMR data with national registers recorded in Statistics Denmark and obtained information on associated factors, such as education and affiliation to the labour market. From the Civil Registration System, information on municipality of residence was recorded. From the National Register of Patients (NRP), information on hysterectomy and bilateral salpingo-oophorectomy was obtained.

National Register of Medicinal Product Statistics

Information in the NRM is categorised according to Anatomical Therapeutical Chemical (ATC) codes. HRT products were extracted under the codes: G02B A03, G03C A03, G03C A04, G03C A53, G03C A57, G03C B01, G03D A02, G03D A04, G03D C02, G03D C03, G03D C05, G03F A01, G03F A12, G03F B01, G03F B05, G03F B06, G03F B09, G03H B01, G03X C01. Additional information on name, trade name, dose, number of packages, defined daily doses (DDD) in 1 package, tablets per package, route of administration (tablet, patch, gel, etc.) and date of redemption was available.

Information on use of drugs for diabetes (insulin (A10A), oral diabetics (A10B)), antiarrhythmics (C01), blood pressure lowering medicine (antihypertensives (C02), diuretics (C03)), beta-blockers (C07), calcium antagonists (C08), drugs influencing renin-angiotensin system (C09) and lipid lowering medicine (C10) was also retrieved from the NRM. Women with 100 DDD or more were categorised as users of the different medicinal products.

First, use of HRT was divided into 45 subgroups by regimen, chemical compound, route of administration and dose (Table I). Based on daily updates from the NRM, a 'hormone exposure line' was constructed for each woman. Each prescription was considered valid from the date the medication was redeemed until the date the DDD expired, and each prescription was allocated to the relevant participants of the 45 subgroups. If another identical prescription (same as the 45 subgroups) was redeemed before the expiration of the last prescription, the duration was extended with the DDD of the new prescription. If an identical prescription was added within 4 weeks after the previous prescription expired, the medication was considered used from redemption of the first prescription until the second expired. If an identical redemption was cashed later than 4 weeks from the last expired, the new prescription was considered valid from the cash date. In case another product of the 45 subgroups was cashed during the same period, that could not be considered a planned combination treatment, it was interpreted as a change in medication, and the new product was counted from the day of redemption. In case of more contemporary 'valid' prescriptions, only one DDD was counted, according to the following rules.

Contemporary redemption of unopposed estrogen or progestagen only therapy *and* combination products was allocated to combination treatment, though the considered dose of the combination therapy was up-regulated one step depending on whether estrogen or progestagen was added. Contemporary redemption of unopposed estrogen and progestagen was considered as 1 of 2 'self-combined therapies' depending on the ratio between estrogen/progestagen dose; cyclic combined therapy if the ratio was <7 and long-cycle therapy if the ratio was between 7 and 14.

The categorisation of 'self-combined' was further subdivided according to route of administration (oral or dermal). A hormonal intrauterine device (hormone-IUD) was considered viable for 3 years. If a new hormone-IUD was redeemed within 5 years from the last IUD, the IUD was considered used in the whole 5-year period. If a hormone-IUD was combined with unopposed estrogen, it was registered

Table I. Hormone replacement therapy classification.

Regimen	Chemical content	Form	Dose		ATC
			Estrogen (mg)	Progestagen (mg)	
I. Unopposed estrogen	Estradiol	Tablet	1	–	G03C A03
		Tablet	2	–	G03C A03
		Tablet	>2	–	G03C A03
		Injection		–	G03C A03
		Plaster	<0.1 mg/day	–	G03C A03
		Plaster	≥0.1 mg/day	–	G03C A03
		Gel		–	G03C A03
	Estriol	Tablet	0.5	–	G03C A04/53
		Tablet	1	–	G03C A04/53
		Tablet	2	–	G03C A53
	Conjugated estrogen	Tablet	0.625	–	G03C A57
		Tablet	1.25	–	G03C A57
II. Progestagen only	Norethisterone	Tablet	–	5	G03D C02
	Medroxyprogesterone acetate	Tablet	–	5	G03D A02
		Injection	–	–	G03D A02
		Suppository	–		G03D A04
	Lynestrenol	Tablet	–	5	G03D C03
III. Cyclic combined estrogen/progestagen	Norethisterone acetate-estradiol	Tablet	1	1	G03F B05
		Tablet	2	1	G03F B05
		Tablet	4	1	G03F B05
		Patch	0.05	≤0.25	G03F B05
	Medroxyprogesterone acetate-estradiol valerat	Tablet	2	10	G03F B06
		Tablet	2	20	G03FB06
	Levonorgestrel-estradiol valerat	Tablet	2	0.75	G03F B01
		Tablet	2	0.25	G03F B09
	Cyproterone acetate-estradiol valerat	Tablet	2	1	G03H B01
	Self combined cyclic	Tablet	–	–	I+II
		Plaster	–	–	I+II
	Self combined longcycle	Tablet	–	–	I+II
		Plaster	–	–	I+II
IV. Continuous combined estrogen/progestagen	Norethisterone acetate-estradiol	Tablet	1	0.5	G03F A01
		Tablet	2	1	G03F A01
		Plaster	0.05	0.17	G03F A01
	Medroxyprogesterone acetate-estradiol valerat	Tablet	1	2.5	G03F A12
		Tablet	1	5	G03F A12
		Tablet	2	5	G03F A12
	Tibolone	Tablet	–	–	G03D C05
	Raloxifene	Tablet	–	–	C03X C01
V. Local treatment	Estradiol	Ring			G03C A03
	Estriol	Vaginal suppository			G03C A04
	Conjugated estrogen	Vaginal suppository			G03C A57
	Dienestrol	Vaginal suppository			G03C B01
VI. Intrauterine device	Levonorgestrel	IUD			G02B A03
	Self combined levonorgestrel-estrogen	IUD- tablet			I+IUD
		IUD- dermal			I+IUD

as combined treatment, and further subdivided according to route of administration of the estrogen in hormone-IUD estrogen oral or hormone-IUD estrogen transdermal.

When one component of a combination therapy expired and was not renewed, only 1 compound treatment was recorded. Other contemporary combinations not previously described as possible

combinations were recorded under the product with the highest DDD, and the prescription with less DDD was neglected.

Local vaginal treatment was only recorded as such if no systemic hormonal compounds had been redeemed contemporarily. Due to the ordination practice of vaginal estrogen, vaginal treatment was considered continuous as long as at least 1/7 DDD was redeemed per day.

Analyses

Our original manuscript included the period 1995–2002, for final analyses the period 1995–2004 was considered.

The 45 subgroups (Table I) were merged into 6 main groups (unopposed estrogen, progestagen only treatment, cyclic combined therapy, continuous combined therapy, hormone-IUD, and local treatment), and the DDD per 1,000 women per day were calculated from the individual exposure lines and subdivided into 5-year age groups for the years 1995, 2002 and 2004.

Medication prescribed in 1995, the first year we had complete information from the NRM, was not considered in the main analyses, as medication redeemed in 1994 but taken in 1995 could not be included, resulting in an underestimation of use in 1995. For 1996, prescriptions redeemed in 1995 but valid in 1996 were included in the 1996 statistics.

The cumulated individual exposure to systemic HRT was calculated for women 50 years old in 1995 (birth cohort 1945), in 1997 (birth cohort 1947), in 1999 (birth cohort 1949), in 2001 (birth cohort 1951), and in 2003 (birth cohort 1953), respectively. These classes were followed for 10, 8, 6, 4 and 2 years, respectively.

Box plots with mean, median, 25% and 75% percentile and minimum and maximum described the distribution of the duration of HRT from 1995 to 2002 in each age group. The analysis of duration of use was made initially for all women in the study, including those who were prevalent users in 1995. Second, we included only those who became incident hormone users in 1996. This distinction was made to evaluate the consequences of our left censored data for the calculated duration of use.

For women aged 55–59 years, the DDD per 1,000 women per day, categorised into the six main groups, was calculated for every year from 1996 to 2004 based on the individual exposure lines.

In assessing time trends, HRT in 1997–2002 was age-standardised to the age-distribution in 1996. Poisson regression analyses were performed to test for time-trends for the two periods, i.e. 1996–2002 and 1996–2004, using the year as the covariate and the expected DDD per 1,000 women per day as outcome. The use of (1) all systemic, (2) continuous combined therapy, and (3) cyclic combined therapy was analysed separately. In addition, for final analyses two Poisson regressions on the share of (1) combined therapy and (2) unopposed estrogen of the total systemic treatment through the period 1996–2004 were conducted.

HRT in DDD per 1,000 women per day for women aged 55–59 years in 2002, was finally correlated to county of residence in Denmark, education and employment status, redemption of other medical products, and the 2 gynaecological surgeries, hysterectomy and bilateral salpingo-oophorectomy.

Results

In 1996, some 938,916 Danish women were 40–69 years old, and 563,021 were 50–69 years old. In 1996, more than 53 million DDD HRT were redeemed, and of these approximately 40 millions in women aged 50–69 years. In 2002, 981,506 women were 40–69 years old, and of this number 623,438 were aged 50–69 years. In 2002, more than 60 million DDD were redeemed, and of these, approximately 47 million were women aged 50–69 years. After 2002, use of HRT more than halved.

HRT regimens according to age

HRT had its peak in women aged 55–59 years, whereas use of local treatment was most prevalent in women above 60 years of age (Figure 1). Hormone IUD were used from age 15 till 54 as apart from being used to diminish bleeding problems, also provides contraception for younger women. Use of unopposed estrogen was quite constant above the age of 50, with about 50 DDD per 1,000 women per day (Figure 1). Combined therapy was most prevalent in women aged 50–59 years, thereafter decreasing.

The majority of women aged 50–54 years on combined treatment were on cyclic combined therapy. Its share was significantly higher in 1996 than in 2002 (Figure 1). With increasing age, the share of cyclic combined therapy was decreasing versus an increasing share of continuous combined therapy.

Hormone regimens in 2002

The peak prevalence of HRT in women aged 55–59 years was 200 DDD per 1,000 women per day (Figure 1). For women aged 50–59 years, approximately 50% of the systemic treatment was continuous combined treatment, 25% cyclic combined treatment, and 25% unopposed estrogen therapy.

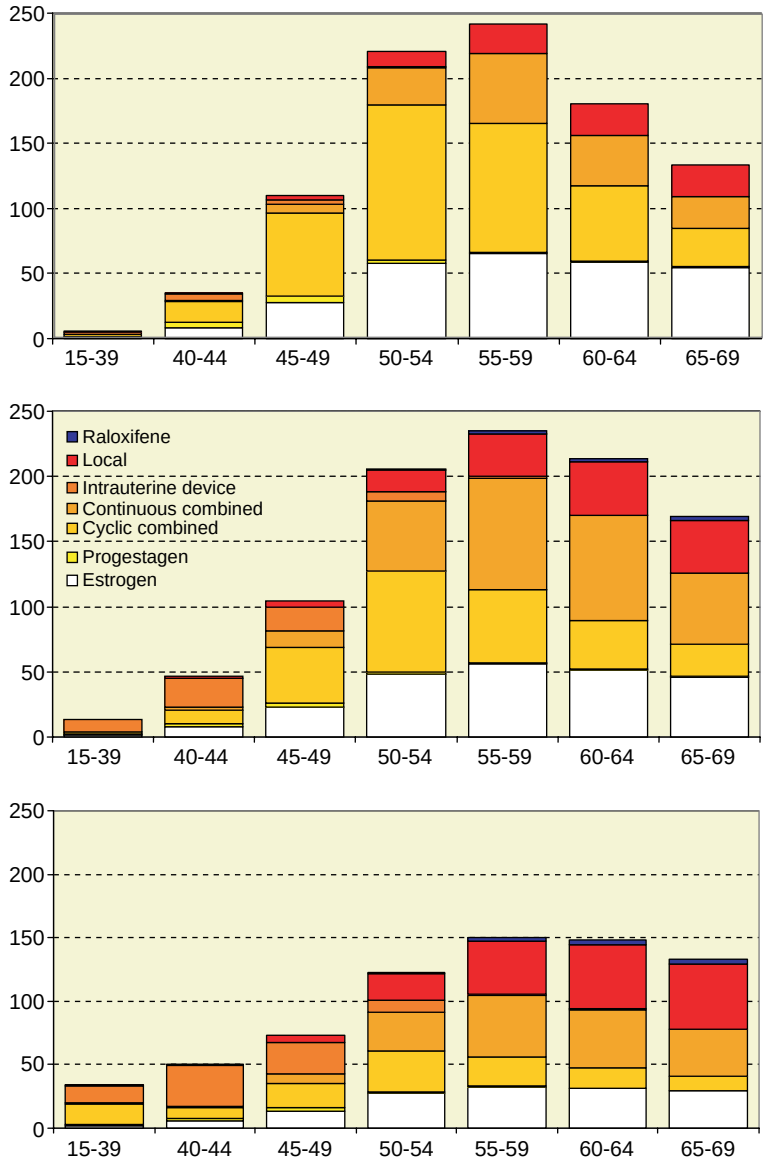

Figure 1. Prevalence of different hormone replacement therapy regimens expressed in defined daily doses per 1,000 women per day sold in Denmark in 1996 (upper), 2002 (middle) and 2004 (lower).

The following sections describe the specific regimens in women aged 55–59 years in 2002.

Unopposed estrogen therapy

The predominant estrogen type was estradiol used by 94.8%. Estradiol-estriol was used by 4.9%, while only 0.3% of women on estrogen therapy used conjugated equine estrogen (CEE).

The most prevalent dose was medium dose (2 mg) used by 71.4% (68.2% oral and 3.2% patch), 14.3% used low dose products (1 mg) (3.4% oral and 10.9% patch), and 2.7% used oral high dose estrogen products (>2 mg). The dose was not determined in 11.3% of women; 9.1% had gels, 1.0% had injection therapy, and 1.2% had estrogen

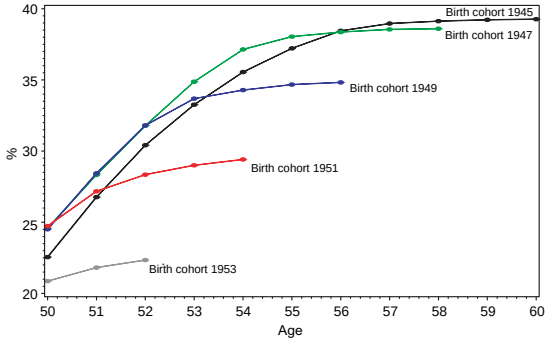

Figure 2. The cumulated prevalence of systemic hormone replacement therapy in women 50 years old in, respectively, 1995 (Birth cohort 1945), 1997 (Birth cohort 1947) 1999 (Birth cohort 1949), 2001 (Birth cohort 1951) and 2003 (Birth cohort 1953) followed since 1995 for, respectively, 10, 8, 6, 4 and 2 years.

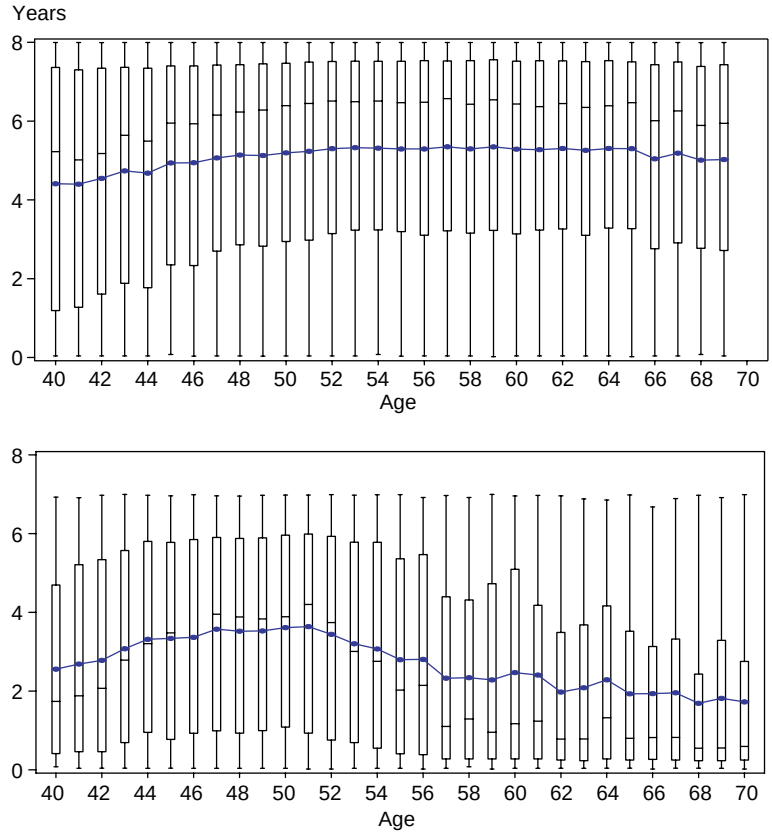

Figure 3. Boxplot on the duration of hormone replacement therapy according to age. The mean is marked as a blue line, the median with a black line in the boxes, 25% percentile lower end of box, 75% percentile top of box and the minimum and maximum value. The upper figure represents prevalent HRT, i.e. women who started HRT during or before 1995 as a function of the age 1 January 1995 ($n = 144{,}595$) followed until the end of 2002. In the lower figure, only incident starters of HRT in 1996 are included ($n = 19{,}398$) and duration is indicated as a function of age on 1 January 1996 followed until the end of 2002.

in combination with hormone-IUD. CEE was used by 0.2% at a dose of 1.25 mg, and in 0.1% at a dose of 0.625 mg.

Cyclic combined therapy

Different progestagen components were used in the cyclic combined treatment. Norethisterone acetate (NETA) constituted 50.5%, cyproteroneacetate (CPA) 5.4%, medroxyprogesterone acetate (MPA) 19.4%, levonorgestrel 13.7%, and 11% were presumed to compose their treatment themselves as they redeemed an estrogen and a progestagen medication contemporarily, administered orally by 4.1% and as transdermal estrogen combined with oral progestagen by 6.9%. The 50.5% cyclic regimens with NETA were administered transdermally by 6.4% in combination with low dose estrogen (50 ug per day) and orally by 44.1%. The 44.1% oral treatment was most often (36.2%) combined with medium dose estrogen (2 mg); 7.8% with high dose estrogen (4 mg), whereas only 0.1% combined with low dose (1 mg) estrogen.

Continuous combined therapy

The predominant progestagen component in continuous combined treatment was 81.5% for the androgen derived NETA, 4.3% contained the progesterone derivate MPA, and tibolone constituted 14.3%. The predominant estrogen dosage in the 85.8% continuous combined therapy, of which 52.3% had 2 mg estrogen, all administered orally, 33.5% had 1 mg estrogen (30.0% oral and 3.5% patch).

Raloxifene

In 2002, raloxifene constituted $<1\%$ of the DDD per 1,000 women per day below age 55, hereafter at age 55–59, 60–64, 65–69, respectively, 1.1, 1.3 and 2.1% of the DDD per 1,000 women per day was raloxifene.

Cumulated HRT exposure

An alternative way to describe the prevalence of HRT is to count the cumulated exposure or how

many women have ever been exposed to HRT at different ages. Figure 2 depicts the cumulated prevalence from age 50 years, subcategorised into birth cohort 1953 with records since age 42, birth cohort 1951 with records since age 44, birth cohort 1949 with records since age 46, birth cohort 1947 with records since age 48, and birth cohort 1945 with records since age 50 years.

Due to the time window, the 1947, 1949 and 1951 birth cohorts initially had more ever users than the 1945 birth cohort, as they were actually followed since their forties, whereas the 1953 had lower ever users. On the other hand, the older cohorts had more years of follow-up, thus the 1945 birth cohort reached 39% ever users of hormones at the age of 57 years. For all classes, the last observation tended to be underestimated, as only those women born on 1 January were observed in a whole year.

Duration of HRT

To illustrate the influence of our time window on the duration calculation, we calculated the duration of HRT in two ways during our initial time window 1995–2002. First, among all women including prevalent hormone users from 1995; and second, we included only women who commenced HRT in 1996. The prevalent hormone users were considered those who redeemed HRT in 1995, including those who started HRT before or during 1995. The incident hormone users were those who started HRT in 1996. The prevalent HRT users ($n =$ 144,595) had a mean duration of HRT of approximately 5 years, and a median of around 6 years in all age groups in our 8-year follow-up period (Figure 3, upper part). The incident hormone users in 1996 (Figure 3, lower part) ($n = 19{,}398$) had maximum duration in women aged 51 years, with a mean of 3.6 years and a median of 4.2 years. There was a larger fraction of short-term users with increasing age as the median length of duration fell with increasing age. Among women aged 50–54 years who were prevalent users in 1995, 11% used it for <1 year, and 63% for 5–7 years. For women starting in 1996, the corresponding percentages were 28% (<1 year) and 39% (5–7 years) (Figure 4).

Trend in HRT from 1996 to 2004

The prevalence of HRT expressed in DDD per 1,000 women per day including continuous combined, cyclic combined, progestagen only, unopposed estrogen, and hormone IUD decreased through the study period (Figure 5). The number of DDD per

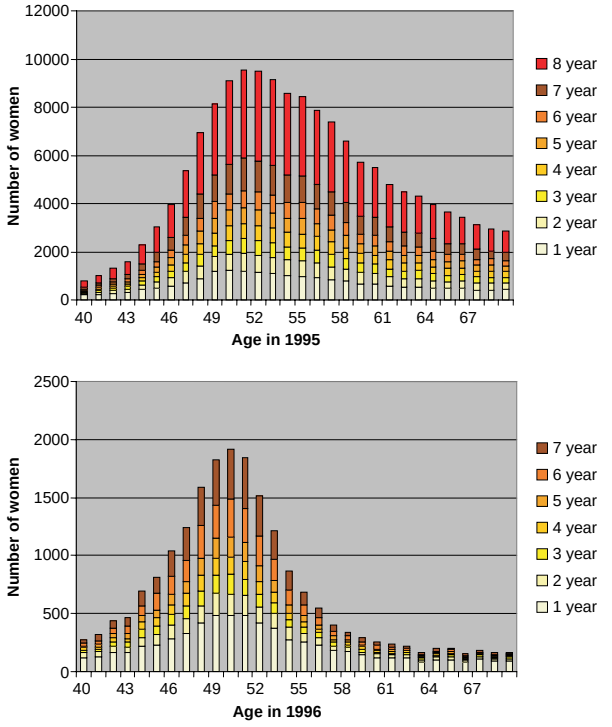

Figure 4. Distribution of the duration of hormone replacement therapy (HRT) in the period 1995–2002 according to the age HRT commences. The upper figure includes prevalent users in 1995, which is women who started during or before 1995, grouped according to maximum recorded length of use. In the lower figure, only women who started HRT in 1996 are included.

1,000 women per day of local treatment was stable throughout the period 1996–2002 (Figure 5).

To test the trends over time, we standardised the population to the age distribution of the population in 1996, and found a significant decrease in systemic treatment by time in the periods 1996–2002 ($p < 0.001$) and 1996–2004 (Table II). From 1996 to 2002, the major change by time was a decrease in use of cyclic combined products ($p < 0.001$) (Table II). After 2002, both the use of cyclic and continuous combined products declined significantly.

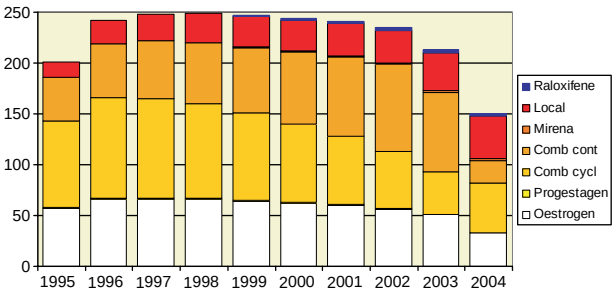

Figure 5. Hormone replacement therapy is defined as daily doses per 1,000 women per day in women aged 55–59 years in 1996–2004.

Table II. Defined daily doses of HRT per 1,000 women per day during the period 1996–2004.

	Standard rate for various regimens		
Year	All systemic	Continuous combined	Cyclic combined
1996	218.0	53.3	99.0
1997	216.9	55.9	96.3
1998	207.8	56.8	88.2
1999	194.3	58.3	77.9
2000	179.8	60.6	72.8
2001	165.9	63.1	53.9
2002	152.3	65.0	42.4
2003	125.3	34.4	30.7
2004	76.5	35.2	16.5

Age distribution standardised to the 1996 population. The estimate from Poisson regression with standardised rate as response and year as covariate is from 1996 to 2002, -0.062 ($p<0.001$) for all systemic, 0.032 ($p=0.196$) for continuous combined, -0.136 ($p<0.001$) for cyclic combined and for the period 1996–2004, -0.0969 ($p<0.001$) for all systemic, -0.0360 ($p=0.0414$) for continuous combined, -0.1736 ($p<0.001$) for cyclic combined.

Characteristics of women on HRT

Use of HRT was associated with education. The lowest DDD per 1,000 women per day was observed among women with only elementary schooling. Thereafter, the use increased with educational length. Among women with a research degree education, however, the use of hormones was again relatively low (Table III).

According to job status, the highest proportion of HRT was observed in women in the labour force. HRT was less prevalent in women treated for diabetes than among women not redeeming diabetes medicine, whereas women on antiarrhythmics, diuretics or other blood pressure lowering medication used hormones a little more frequently than women without this medical use. HRT was not correlated to use of lipid lowering agents.

Geographical variation

HRT was not equally distributed in all areas in Denmark (Figure 6). In women aged 55–59 years, those living in the urban area, the Frederiksberg community had the highest prevalence of 285 DDD per 1,000 women per day. The lowest prevalence was found in the rural Ringkøbing County with 192 DDD per 1,000 women per day.

Discussion

We found HRT most prevalent in women aged 55–59 years, with an average of 200 DDD per 1,000 women per day in 2002. In women aged 50–57 years, 39% had ever been exposed to HRT. In comparison, based on questionnaires, the one million women study in England in the same period found that among women aged 50–69 years, 50% ever used hormones (3). In an American representative cohort of women, 52% of women aged 48–57 years had ever been on hormones in 1992 (4). Our 39% ever on HRT would possibly have increased to

Table III. Defined daily doses (DDD) of hormone replacement therapy per 1,000 women per day among women aged 55–59 years in 2002 according to education, employment, and redeemed other medications (ATC codes)

	DDD/1000/day
Education	
Elementary school	209
Occupational practice	240
High school	267
Technical high school	270
Short-term education	271
Middle-term education	273
Bachelor	305
University degree	295
Research degree	210
Unknown	212
Employment	
Employed	240
Unemployed	230
Outside	215
Insulin (A10A)	
No	235
100–364 DDD	150
>365	173
Oral antidiabetics (A10B)	
No	237
Yes	131
Heart medication (C01)	
No	234
Yes	269
Diuretics (C03)	
No	227
Yes	262
Blood pressure lowering	
No	229
Antihypertensive (C02)	248
Beta blockers (C07)	272
Calcium antagonist (C08)	259
Renin-angiotensin inhibitor (C09)	253
Lipid lowering (C10)	
No	235
Yes	225
Hysterectomy	
No	216
Yes	374
Bilateral salpingo-oophorectomy	
No	227
Yes	483

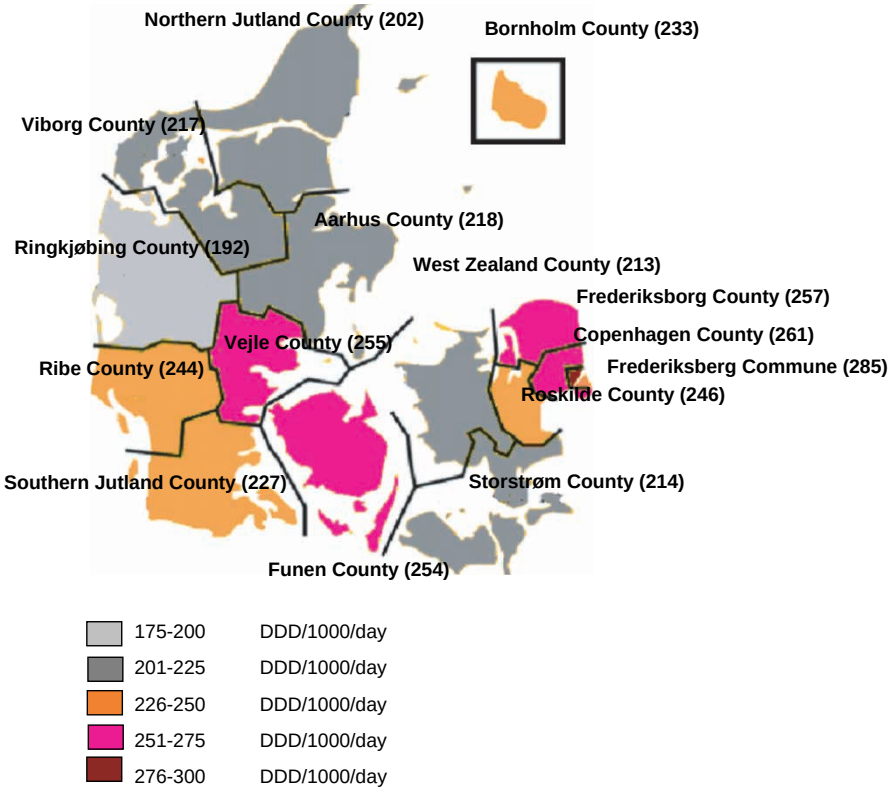

Figure 6. Defined daily doses of hormone replacement therapy per 1,000 women per day for women aged 55–59 years in 2002 according to Danish Counties. Frederiksberg municipality and Copenhagen municipality are not part of Copenhagen County.

the same level if we had a broader time window than 7 years. However, the Danish Nurse Cohort Study based on questionnaires and no time window found approximately the same fraction of ever-users as we did (5).

We found the majority of women ever exposed to HRT used it either <1 year, or for longer periods, i.e. more than 5 years. We made this conclusion despite the fact that our data were left-censored, as we could evaluate the fraction of long-term users among the prevalent users of HRT in 1995, and the short-term use among the women who started HRT in 1996.

Although left-censored, our data are in accord with not left-censored studies, which in England and Norway found a mean duration of HRT of 4.9 years (3,6) and in the US of 6.6 years (4). These studies found shorter median duration. The Danish Nurse Cohort study found that 70% of women on HRT were still using hormones 5 years after start of therapy, 57% after 10 years, and 48% after 15 years (5), findings in accord with our polarised duration pattern.

We found that about two-thirds of women used combined regimens, and around one-fourth used unopposed estrogens. In comparison, the MWS found 41% on estrogen only therapy. The vast majority of Danish women on unopposed estrogen therapy used estradiol products. Conjugated estrogens are used more frequently in England and especially in the US. Our predominant progestagen component in combined regimens was NETA, constituting 79% of the continuous combined regimens, and 51% of the cyclic combined regimens. In the US, MPA dominates the market.

We observed a modest decline in the use of HRT after 1998, mainly due to a decrease in cyclic combined therapy. In 1998, the first randomised clinical trial on continuous combined HRT versus placebo-the HERS study-was published demonstrating no protective effect of having a new myocardial infarction after having an event of coronary heart disease (1). The decline in the use of HRT in western countries was further accelerated after the publication of results from the Women's Health Initiative Study in July 2002 (2). They found an increased risk of cardiovascular disease in a placebo-controlled trial on continuous combined HRT. Subsequently, there was a further decrease in the use of hormones (7). In our study, use of HRT was reduced to 65%.

We found geographical variations in the prevalence of HRT, ranging from 19 to 28% on hormones. Data from the UK (3) have demonstrated less regional variation in the current use of hormones, ranging from 30% in Scotland to 35% in South East England around London.

In contrast to the UK and the US (4), where a significant educational gradient in the use of hormones is present, we found only minor, and less consistent differences, possibly because the social impact of different levels of education in Denmark is less pronounced than in the UK and US.

The less frequent use of hormones in women with diabetes was also demonstrated in the MWS. They also found less use among women on heart or antihypertensive medicine (3), contrary to our finding of a slightly more prevalent use in these groups. The higher prevalence of HRT in women with a hysterectomy or oophorectomy has been a consistent finding (3,4).

Some limitations of our study should be mentioned. First, we had a time window implying exposure misclassification due to truncation of the database in 1995 is not recorded. Second, we do not know to what extent redemption of a HRT prescription indicates that the hormones are actually taken. This source of error would tend to overestimate HRT. We previously investigated this subject among Danish nurses and found a sensitivity of 78.4% (95% CI: 75.4–81.4), and a specificity of 98.4% (95% CI: 97.8–98.9) of self-reported current HRT considering pharmacy databases as the golden standard. Women recorded in pharmacy databases but did not report HRT themselves affected the sensitivity. It was found that of these 'false negative' users of hormones, 41% had only redeemed 1 prescription, and 43% had redeemed 2–5 prescriptions (8). Thus, this potential bias is present mainly in women who have only had one or few prescriptions, and probably does not affect our estimates in women with repeat prescriptions.

Third, medication brought abroad could underestimate the use. We do not believe that it is a serious problem in the study period, as the refund systems in Denmark makes it favourable to buy medication in Danish Pharmacies.

In conclusion, some women could receive HRT without a prescription, in a clinical trial for instance, and this would also underestimate the use. This potential bias has, however, only a very limited quantitative impact.

Our study also has some strengths. An important strength is that the whole Danish population was included. Consequently, no selection bias of being a participant in a scientific study is present. There is no recall bias. The large sample permits stratified analyses also on compounds with a little marked share.

Also, our coding rules attempted to take account of situations known from daily clinics as change of medication, self-combined treatments etc. We had no possibilities to validate the rules, but we made a calculation on how our coding rules for HRT use affected the DDD. The amount of prescribed HRT in the 1995–2002 study periods was 494 million DDD. After allocation according to our rules, some DDD were removed and others were added. In total, 99 million DDD were changed. In the unopposed estrogen and progestogen, 23% and 44% of DDD were ignored, respectively, whereas in the local treatment group, 111% DDD were added due to the fact that many women take <1 DDD per day.

For systemic combined estrogen-progestagen therapy, $<4\%$ were altered. DDD were reduced due to the prescribing of a new product before the expiration of the previous product. DDD were added by filling out gaps of less than 4 weeks between two prescriptions. For hormone-IUD users, 48% DDD were changed. Reductions were made in case of prescribing a combined therapy before the expiration date, DDD were added to the standard of 3 years if a new hormone-IUD was prescribed within 5 years after the last prescription.

Conclusion

In the study period 1995–2002, a substantial fraction of the Danish female population was exposed to HRT for longer periods. Use of HRT is associated with circumstances associated with health.

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