Results

PART 1: DESCRIPTIVE EPIDEMIOLOGICAL STUDIES

1. The utilization of steroid hormones in the general population

1.1 Use of steroid hormones for contraception and for HRT

As a vast majority of participants in the five National Health Surveys were under ambulant care, steroid hormones, therefore, were mainly used for the purpose of contraception and HRT other than for the treatment of various gynecological diseases (Table 8). In contrast to the use of steroid hormones for contraception, the proportion of which declined in all steroid hormone indications from 1984 to 1999 in the western part of Germany, the use of steroid hormones for HRT as well as its proportion in all steroid hormone indications increased steadily. In the eastern part of Germany, the same trend on steroid hormone use from 1991 to 1999 was observed as its western counterpart, namely more and more steroid hormones were used for HRT, both the number of users and the proportion in all steroid hormone indications were greatly increased (Table 8).

Table 8: Female sex hormone users and the use rate in women population in the five German National Health Surveys from 1984 to 1999

| Surveys	Women popula-tion	Indications of hormones in female users				Use rate in women population (%)		
		OC(%)	HRT(%)	Others(%)	Total(%)	OC	HRT	Total
T0 1984-1985	2373	258(80.4)	46(14.3)	17(5.3)	321(100)	10.87	1.94	13.53
T1 1987-1988	2686	353(77.1)	81(17.7)	24(5.2)	458(100)	13.14	3.02	17.05
T2 1990-1991	2688	328(57.7)	210(37.0)	30(5.3)	568(100)	12.20	7.81	21.13
T3 1991-1992	1160	303(82.3)	63(17.1)	2(0.6)	368(100)	26.12	5.43	31.72
BGS98 1998-1999	3674	620(58.3)	427(40.1)	17(1.6)	1064(100)	16.88	11.62	28.96
East	*1266*	*264(69.8)*	*110(29.1)*	*4(1.1)*	*378(100)*	*20.85*	*8.69*	*29.86*
West	*2408*	*356(51.9)*	*317(46.2)*	*13(1.9)*	*686(100)*	*14,78*	*13.16*	*28.49*
Total	**12581**	**1862(67.0)**	**827(29.8)**	**90(3.2)**	**2779(100)**	**14.80**	**6.57**	**22.15**
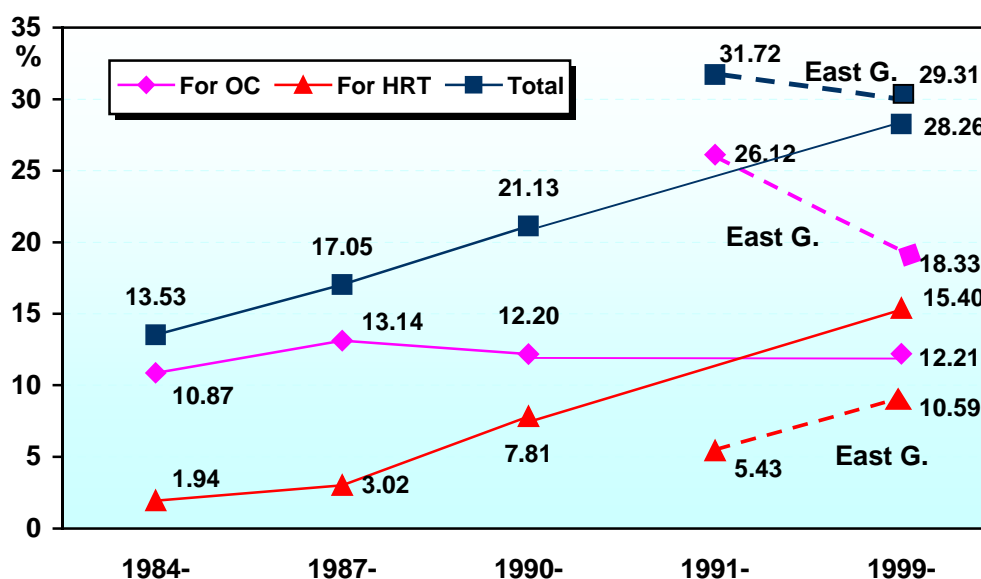
Fig. 3: Trends of use of steroid hormones for contraception and for HRT in German women aged 25-69 from 1984 to 1999

Use rate of steroid hormones in general female populations

Because of the age difference in the study populations between survey BGS98 and the other four surveys and the huge socioeconomic differences between the former German Democratic Republic (GDR, East Germany) and German Federal Republic (West Germany), the use rate in Table 8, strictly speaking, could not be compared simply with each other. So, hormone users were separately identified in specific age groups for participants of surveys T0-T3 as well as in East Germany and West Germany for participants in survey BGS98. Table 9 (Page 113) and Table 10 (Page 114) show the age-specified use rate for contraceptives and for HRT, from which we could in survey BGS98 figure out 428 (East 187, West 241) and 412 (East 108, West 304) women aged 25-69 years who used steroid hormones for contraception and for HRT, respectively. Therefore, in survey BGS98, for women aged 25-69 years the total use rate of steroid hormones was 28.62% (East 29.31%, West 28.26%) and the use rate for contraceptives and for HRT were 14.3% (East 18.33%, West 12,21%) and 13.8% (East 10.59%, West 15.40%), respectively. Fig. 3 shows the trends of use rate of steroid hormones in the German women population of the same 25-69 years of age with the comparison between the former East Germany and West Germany. In West Germany from 1984 to 1999, the use of steroid hormones increased steadily from 13.5% to 28.26%. While the prevalence rate of contraceptives use changed

very little (10.9% to 12.21%), the use of steroid hormone for HRT rose dramatically from 1.9% to 15.4% in the female population aged 25-69, contributing far most to the increase of steroid hormone use. In East Germany for survey T3, the use rate of steroid hormones was as high as 31.72%. Yet most of the women (82.3%) used steroids as contraceptives, the use of which declined greatly from 26.12% in 1991 to 18.33 in 1998, which was, however, still much higher than that of their western counterpart (12.21%). The use for HRT doubled from 5.43% to 10.59% in the last ten years (Fig. 3).

Use rate and age

Fig. 4 shows the use rate of steroid hormones for contraception and for HRT in each survey along with age. Quite naturally, the use of contraceptives in general populations declined along with age till 54 years old in all five surveys, whereas the use of HRT displayed a bell-shaped distribution along with age, peaking at the 50-59
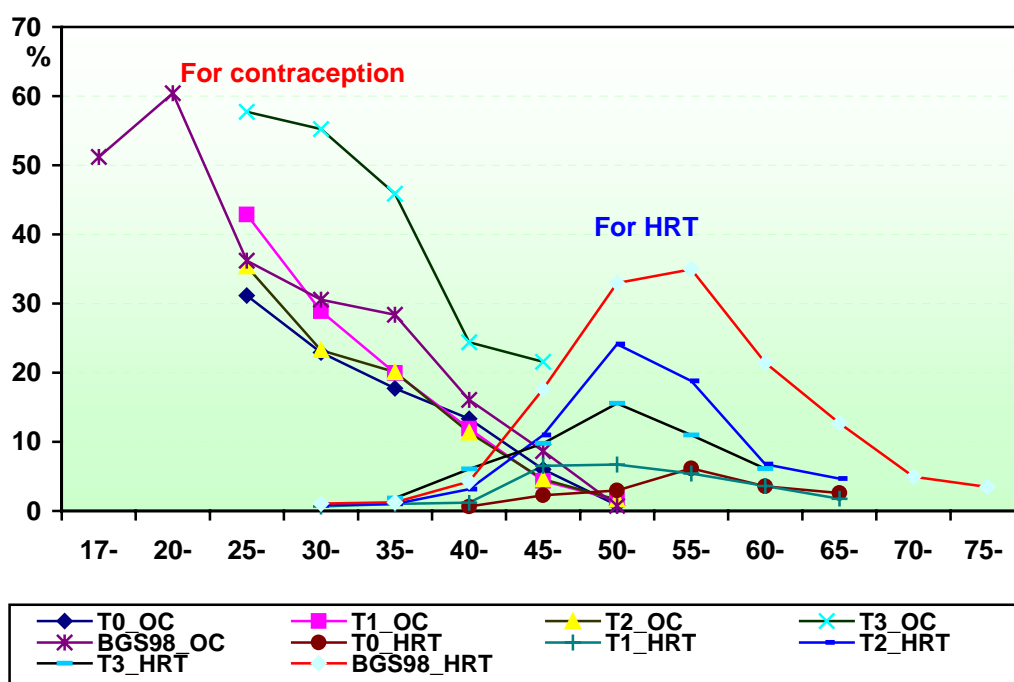

Fig. 4: Age-specified use rate of steroid hormones for contraception and for HRT in the five German National Health Surveys

year-group, in which most women will experience their climacteric years (Fig. 4). From Table 9 and Table 10, we also could figure out the use rate of OC use in women aged 25-54 years, the sex-active population in the actual need of contraceptives, namely 15.06%, 18.65%, 16.74%, 35.56% and 20.94% (East

27.91%, West 17.54%) in survey T0, T1, T2, T3 and BGS98, respectively (Table 9).
Very few women younger than 40 years old used HRT, the prevalence rate of HRT
use for women aged 40-69 years was 2.95%, 4.41%, 12.34%, 8.71% and 21.23%
(East 15.82%, West 24.13%) in survey T0, T1, T2, T3 and BGS98, respectively
(Table 10). In addition, for survey BGS98, 57.0% (192/337) women aged 18-24 years
used contraceptives and 18.64% (419/2248) women aged 40-79 years were on HRT.

Use rate and body mass index (BMI)

The BMI-specified use rate in each survey shows a decline trend for contraceptives
and a rather plain curve for HRT along with the increase of BMI. For a specific BMI-
class, the use rate of contraceptives in T3 was much higher than in the other four
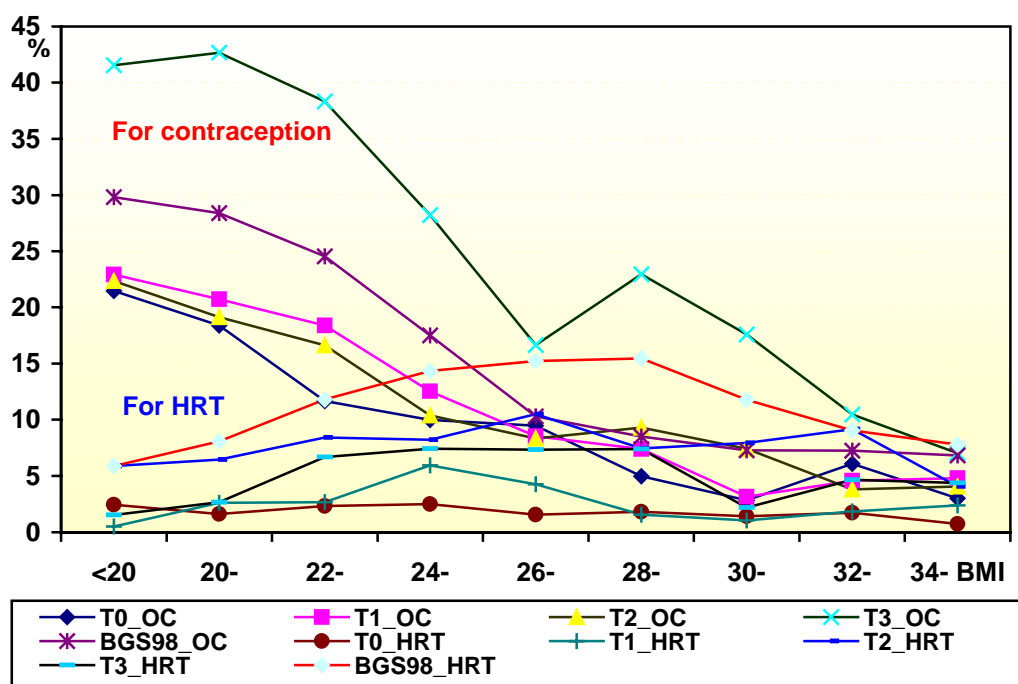surveys (Fig. 5).

**Fig. 5: BMI-specified use rate for contraceptives and for HRT in the
five German National Health Surveys**

Use rate and education

Women with primary school education used less contraceptives compared with
women with middle and higher education. There were no marked differences in the
contraceptives use rate between women with middle and women with higher
eduation in the first three surveys though their contraceptive use rates were much

higher than that of women with primary education in survey T3 and BGS98. Surprisingly, we did not find an increase trend along with school education for HRT use. In fact, the HRT use in higher-educated women was less than that of middle and primary educated women in each survey (Fig. 6).
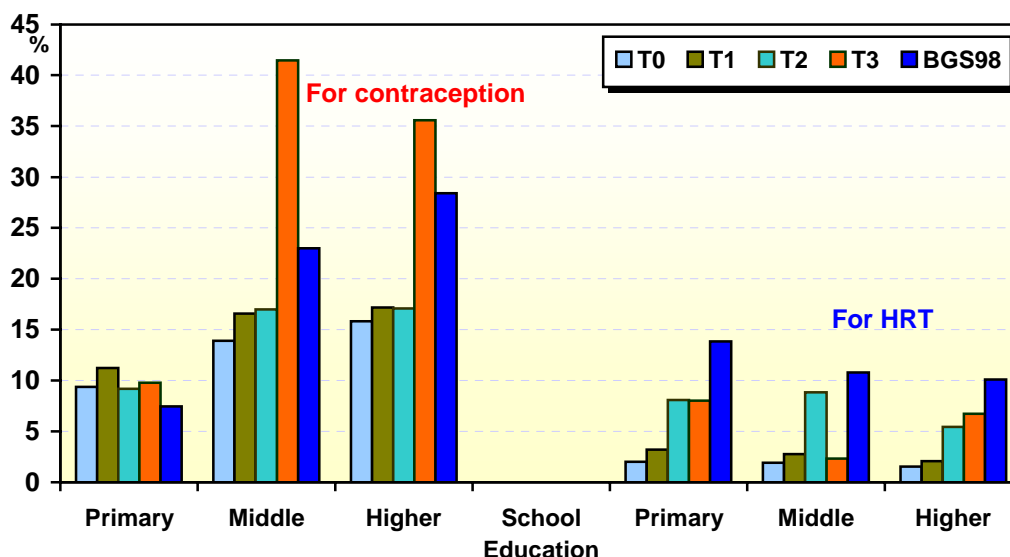

Fig. 6: Use rate of steroid hormones for contraception and for HRT in the five German National Health Surveys-classified by school education

Use rate and household income

According to the monthly net income of a household, low-, middle- and high-income household could be classified at large, corresponding to net income per month 'under
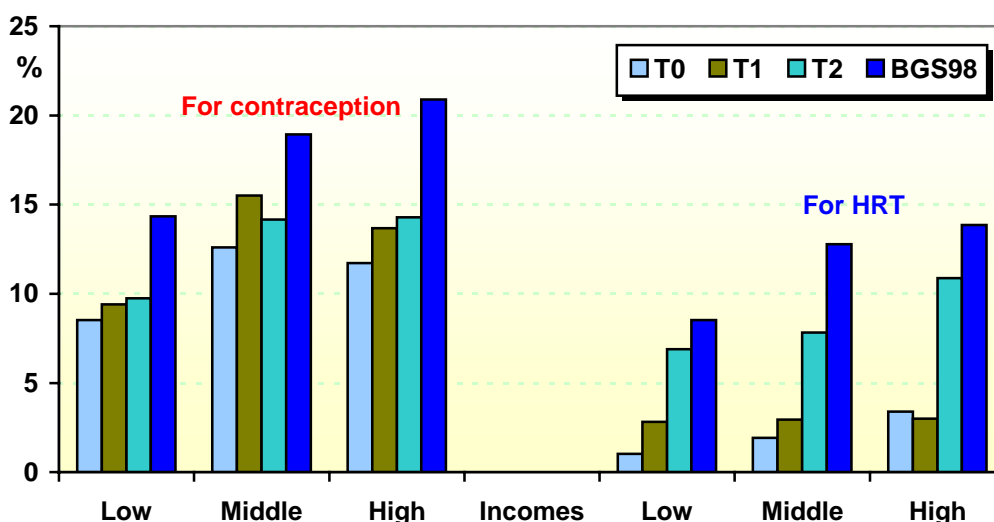

Fig. 7 : Use rate of steroid hormones for contraception and for HRT in the four German National Health Surveys---classified by household income

2000 DM', '2000-4000 DM' and 'over 4000 DM' for surveys T0-T2 and 'under 2500 DM', '2500-5000 DM' and 'over 5000 DM' for survey BGS98. Low-, middle- and high-income population accounted for approx. 30%, 50% and 20% of total population in each survey. Data for survey T3 were unavailable. Fig. 7 shows clearly the association of the use of steroid hormones for HRT with the household income in surveys T2 and BGS98. The higher household income, the more HRT use. For contraceptive use, however, those with a higher income were comparable with those who had a middle income.
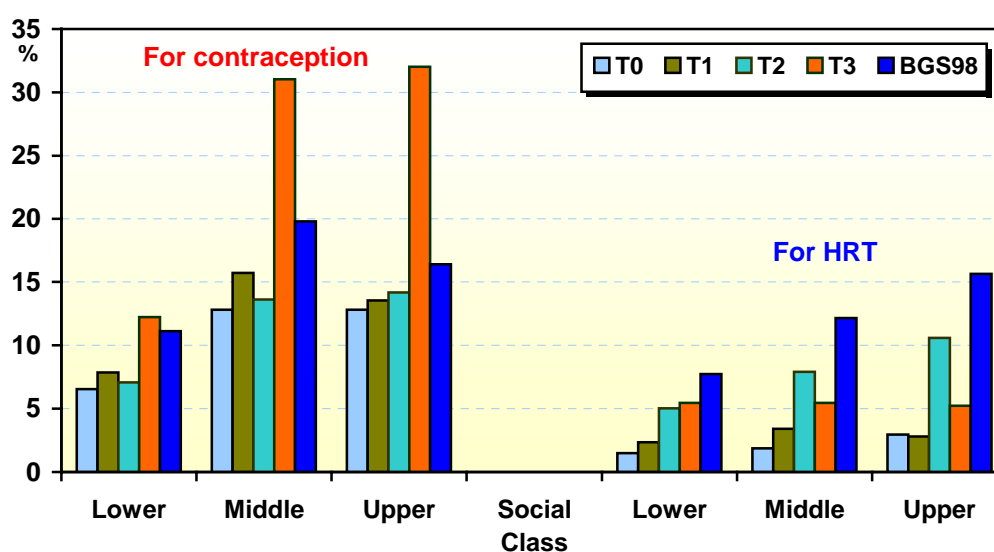

Fig. 8: Use rate of steroid hormones for contraception and for HRT in the five German National Health Surveys-classified by social class

Use rate and social class

Social class was a comprehensive concept for the education, profession and income of a participant. According to Hoffmeister [95], 7 scales were ranked for the education, profession and income of participants, the higher the scale, the higher the social class. Overall, social class was largely grouped as lower, middle and upper class when the above three scales are added together. Like Fig. 7, Fig. 8 shows the same trend regarding the association of the use of steroid hormones with social class. Either for contraception or for HRT, the use of steroid hormones in lower social class as well as in those with low income was less than that in middle and upper social classes as well as in those with a higher income in each single survey. Unlike contraceptives, the use of which in upper class was comparable with or even lower

than that in middle class, the use of steroid hormones for HRT showed a linear increase trend from lower to upper social class, particularly for survey T2 and BGS98 with relative large sample size.
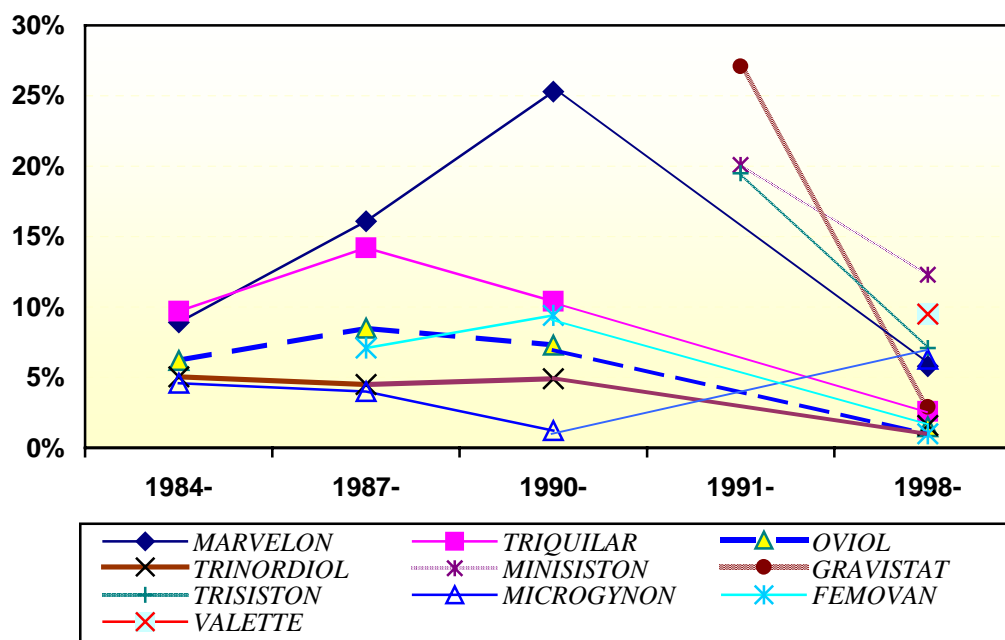

Fig. 9: Change of market shares for the ten most frequently used contraceptives in the five German National Health Surveys from 1984 to 1999

1.2 Pharmaceutical products used for contraception and for HRT

1.2.1 Oral contraceptives

Totally,154 contraceptive products (including 3 products that were usually used for HRT) were identified from all five surveys according to their components and dose of components. 39, 44, 41, 14 and 47 contraceptives were used in survey T0, T1, T2, T3 and BGS98, respectively. All products together with their components and doses are listed in the appendix 2.

The most frequently used oral contraceptives from 1984 to 1999 (Table 11).

Fig. 9 shows the change of market shares for the ten most often used contraceptives of all five surveys from 1984 to 1999 in Germany. Because the market in the former East Germany and West Germany were independent from each other, some products were unavailable for nonresidents. After reunification of the two parts of Germany, the market share for each product declined greatly in 1998 except for

MICROGYNON, which had a higher market share of 6.3% compared with 1.22% in 1990. VALETTE was available in survey BGS98 only with market share of 9.5%. The ten most frequently used contraceptive products accounted for 56.2%, 66.3%, 75.0%, 98.3% and 61.9% all contraceptive use in survey T0, T1, T2 T3 and BGS98, respectively (Table 11, Page 115).
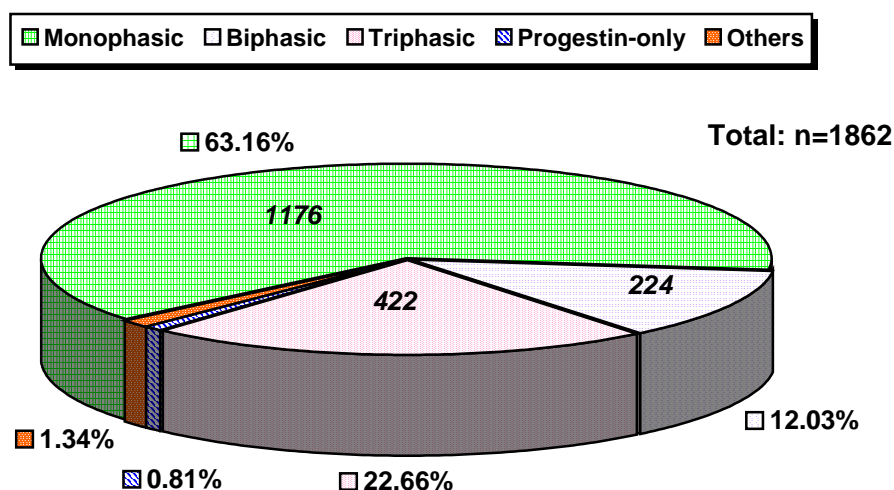

Fig. 10: Profiles of all contraceptives used in the five German National Health Surveys

Profiles of oral contraceptive products

Of all contraceptives use, mono-, bi-, and triphasic contraceptives accounted for 63%, 12% and 23%, respectively. Progestogen-only contraceptives were used rarely
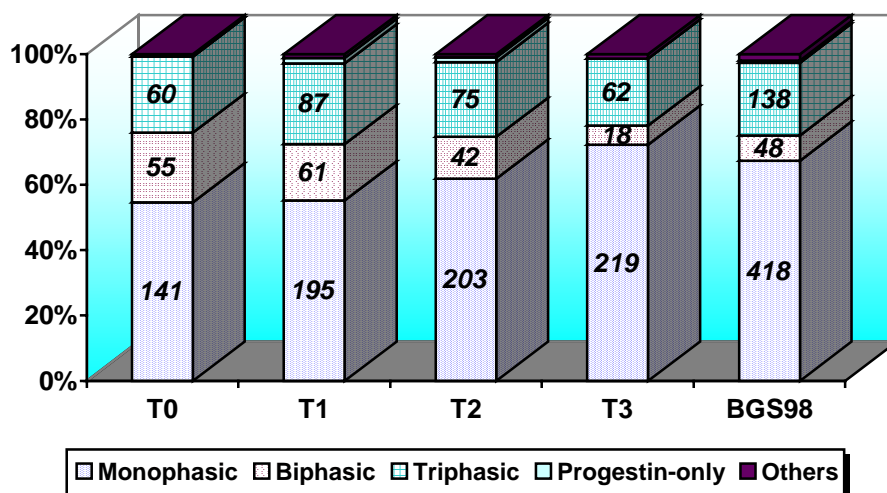

Fig. 11: Profiles of oral contraceptives used in the five German National Health Surveys from 1984 to 1999

and accounted for 0.81% (Fig. 10). In the five surveys from 1984 to 1999, the use of monophasic contraceptives increased steadily from 141 to 418 with the proportion of 54.7% in survey T0 and 66.3% in survey BGS98 (in survey T3 this proportion was 72.3%); whereas the proportion of biphasic contraceptives decreased from 21.3% to 7.7% (T3: 5.9%). The proportion of triphasic contraceptives essentially remained constant (22.3-24.6%; T3: 20.5%), though the absolute number of triphasic contraceptive use doubled (Fig. 11).

Profiles of estrogens used in oral contraceptives

Usually, together with various progestins, ethinyl estradiol and mestranol were used as estrogens in combination contraceptives. Of all oral contraceptives, 93.4%, 95.5%, 96.0%, 89.1% and 96.3% products contained ethinyl estradiol while only 6.2%, 2.55%, 2.1%, 9.9% and 1.45% products used mestranol as estrogen component in survey T0, T1, T2, T3 and BGS98, respectively (Fig. 12). Less mestranol-containing contraceptives were used in the last survey than ever before. Category 'others' in Fig. 12 included progestogen-only contraceptives, HRT products (used for contraception) and contraceptives whose components were not clearly specified.
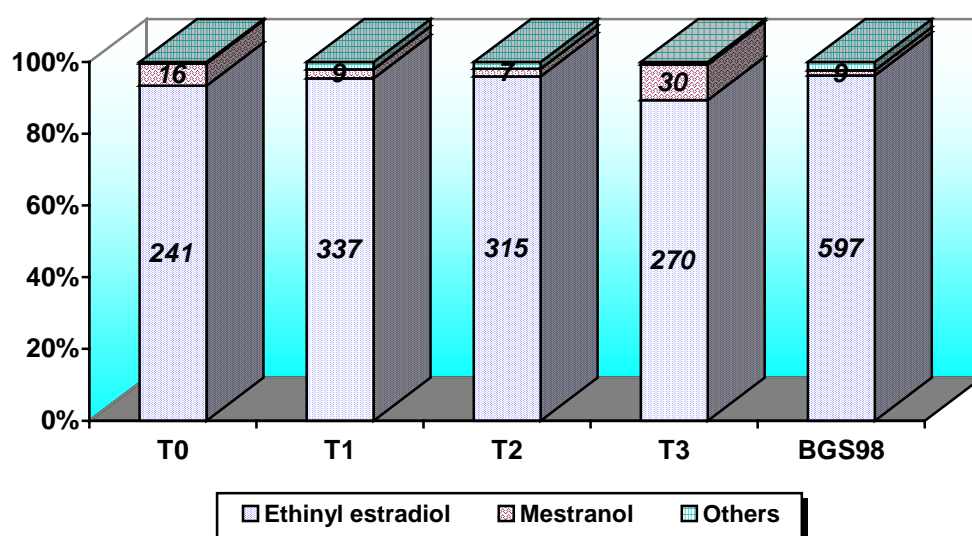

Fig. 12: Estrogen profiles of oral contraceptives used in the five German National Health Surveys from 1984 to 1999

Dose of estrogens in combination contraceptives

In combined OCs of five surveys, the most often used dose of estrogens was 15-50 µg ethinyl estradiol or 50-100 µg mestranol for every single use. In addition, there were 5 women who used HRT products for contraception, the dose of which was 1-2 mg estradiol; and 2 women used DEPOSISTON, which contained 1 mg ethinyl estradiol.

As to be expected, high-dose ethinyl estradiol (>=50 µg) contraceptives were more often used in the earlier survey T0 and in the survey T3. Their use and fraction in each survey tended to decline along with time from 43.6% (105/241) in 1984 to 12.5% (74/590, 7 contraceptives were not specified) in 1998 while the use of low-dose ethinyl estradiol (<50 µg) contraceptives increased from 56.4% in 1984 to 87.5% in 1998 (Fig. 13).
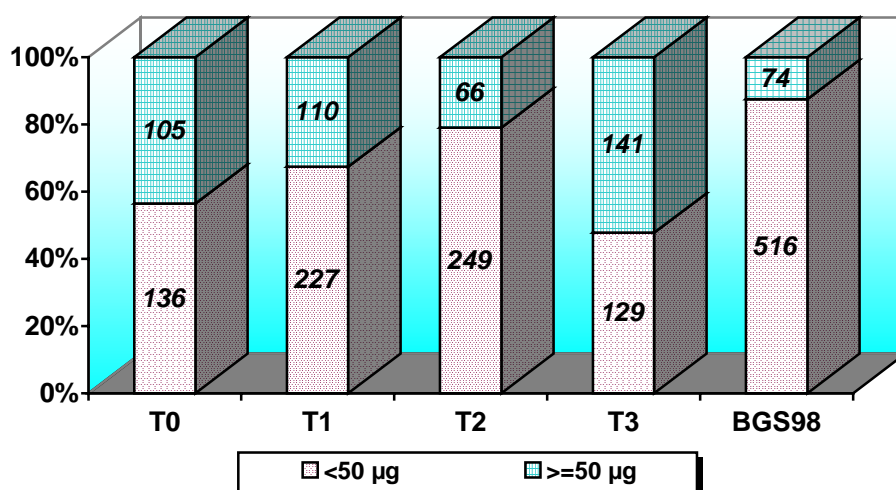

Fig. 13: High-dose(>=50 µg) and low-dose (<50 µg) ethinyl estradiol-containing contraceptives used in the five German National Health Surveys from 1984 to 1999

Progestogens used in contraceptives

Totally 11 progestogens were used in combined or progestogen-only contraceptives, of which levonorgestrel (47.1%, 869/1844), desogestrel (16.9%, 314/1844), norethisteron (10.8%, 200/1844) and lynestrenol (7.7%, 142/1844) were most often used. Norgestimat and norgestrel were used only rarely and ethynodiol was no longer available in survey T3 and BGS98 (Table 12). The use of gestodene and

desogestrel, two progestins of the 'third-generation' contraceptives, tended to decline after they reached their peak in 1990. In contrast, the use of levonorgestrel and chlormadinone tended to increase, while lynestrenol showed a declined trend of use.

Table 12: Progestogens used in all contraceptives from the five German National Health Surveys*

Progestins	National Health Surveys n (%)					Total
	T0	T1	T2	T3	BGS98	n (%)
Levonorgestrel	103(11.9)	127(14.6)	93(10.7)	203(23.4)	343(39.5)	**869(100)**
Desogestrel	40(12.7)	89(28.3)	108(34.4)	1(0.3)	76(24.2)	**314(100)**
Norethisteron	48(24.0)	36(18.0)	25(12.5)	62(31.0)	29(14.5)	**200(100)**
Lynestrenol	53(37.3)	52(36.6)	32(22.5)		5(3.5)	**142(100)**
Gestodene		32(35.2)	40(44.0)	2(2.2)	17(18.7)	**91(100)**
Chlormadinone	9(10.6)	4(4.7)	6(7.1)	30(35.3)	36(42.4)	**85(100)**
Dienogest				3(4.8)	59(95.2)	**62(100)**
Norgestimat		7(20.0)	16(45.7)	1(2.9)	11(31.4)	**35(100)**
Cyproteronacetate					27(100)	**27(100)**
Norgestrel	3(20.0)	3(20.0)	7(47.7)		2(13.3)	**15(100)**
Ethynodiol	1(25.0)	2(50.0)	1(25.0)			**4(100)**
Total	**257**	**352**	**328**	**302**	**605**	**1844**

Excluding 18 unspecified contraceptives

1.2.2 HRT products

According to the components and their doses, a total of 104 hormone products (including 12 oral contraceptives) were used for HRT in the five German National Health Surveys. 21, 32, 37, 24 and 68 HRT products were used in survey T0, T1, T2, T3 and BGS98, respectively. All HRT products together with their components and doses are listed in the appendix 3.
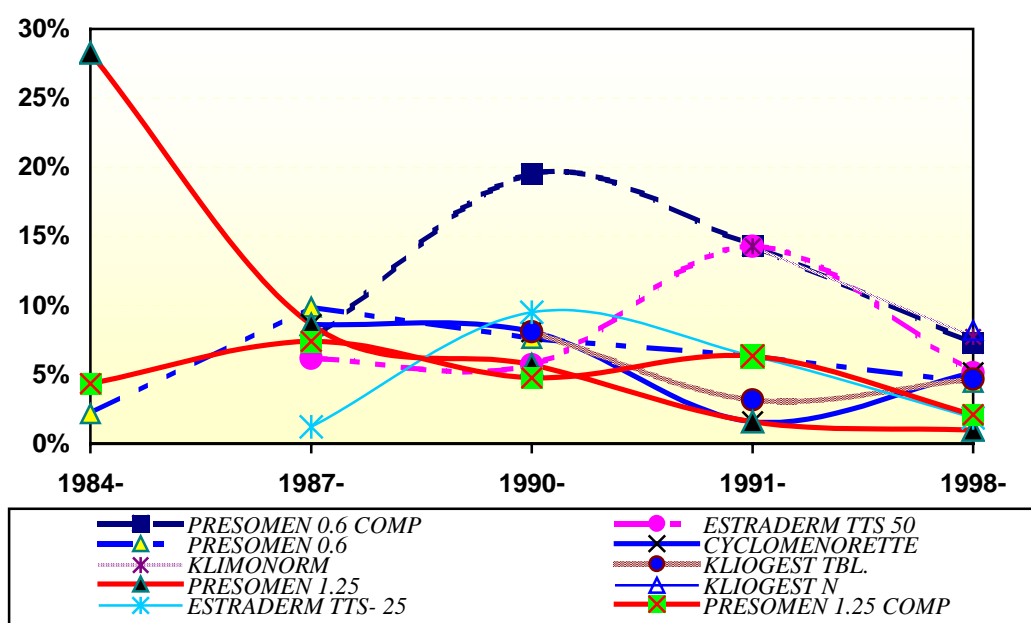
Fig. 14: The change of market shares for the ten most frequently used HRT products in the five German National Health Surveys from 1984 to 1999

The most frequently used HRT products from 1984 to 1999 (Table 13, Page 116)

Fig. 14 shows the change of market shares of the ten most frequently used HRT products from 1984 to 1999 in Germany. Similar to OCs, the market share for each HRT product declined greatly after the reunification of East Germany and West Germany. ESTRADERM TTS 50 and ESTRADERM TTS-25 were two plasters containing low-dose of 4 mg and 2 mg estradiol and released estradiol amounts of 0.05 mg and 0.025 mg estradiol per day, respectively. The ten most frequently used HRT products in each survey accounted for 76.09%, 65.43%, 77.14%, 74.60% and 54.57% all HRT use in T0, T1, T2, T3 and BGS98, respectively (Table 13). In 1984, there were less HRT products to be chosen and the estrogen-only product, PRESOMEN 1.25, accounted for 28.26% all HRT use, by far exceeding the use of any other HRT product. In the last survey of BGS98, estrogen plus progestin HRT products, KLIOGEST N, KLIMONORM; PRESOMEN 0.6 COMP and CYCLO-MENORETTE were more often used than ever before. KLIOGEST N was available only in the survey BGS98 with a market share of 8.2% (Table 13, Page 116).
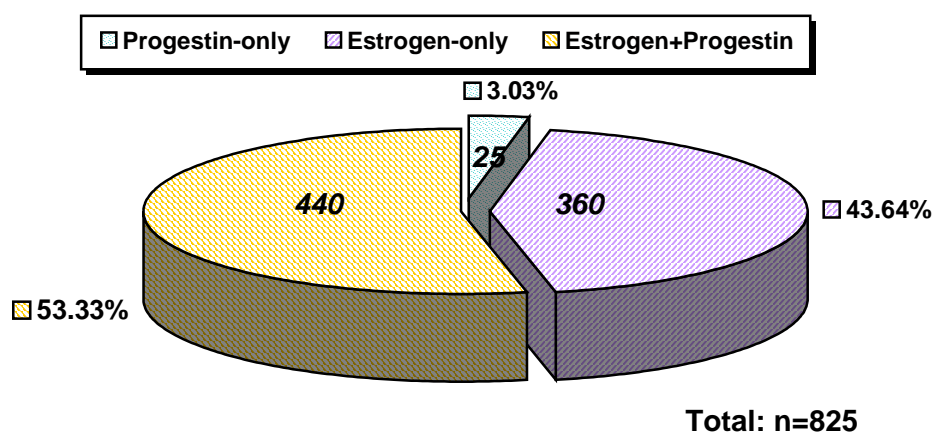
Total: n=825

**Fig. 15: Profiles of all HRT products used in the five German
National Health Surveys**

Profile of HRT products in the five National Health Surveys

Of all HRT products in the five German National Health Surveys, estrogen-only and estrogen plus progestin products accounted for 44% and 53%, respectively. The other 3% were progestin-only products, most of them were used for short-term only (Fig. 15). 2 cases were not specified. However, the proportion of the two regimens in each survey changed greatly from 1984 to 1999 (Fig. 16). In the earlier time, estrogen-only products were more often used than estrogen plus progestin products with the proportion of 78.3% (36/46) in survey T0 and 54.3% (44/81) in survey T1. In sharp contrast, estrogen plus progestin products were more often used in the last survey BGS98, the proportion of which increased from 19.6% (9/46) in survey T0 to 58.8% (251/427) in survey BGS98 (Fig. 16). This reflects the awareness of the risks of endometrial cancers which can be reduced by the combination with progestogens.

Of all HRT products, CEE-containing products accounted for 30.6% (253/827), demonstrating a declining trend from 1984 to 1999 (CEE-containing products accounted for 47.8% (22/46), 40.7% (33/81), 40.0%(84/210), 31.7% (20/63) and 22.0% (94/427) in survey T0, T1, T2, T3 and BGS98, respectively) whereas chemically synthesized estrogens accounted for 64.4% (533/827), demonstrating an increased trend from 1984 to 1999 (50.0% (23/46), 59.3% (48/81), 56.7% (119/210), 60.3% (38/63) and 71.4% (305/427) in survey T0, T1, T2, T3 and BGS98, respectively).
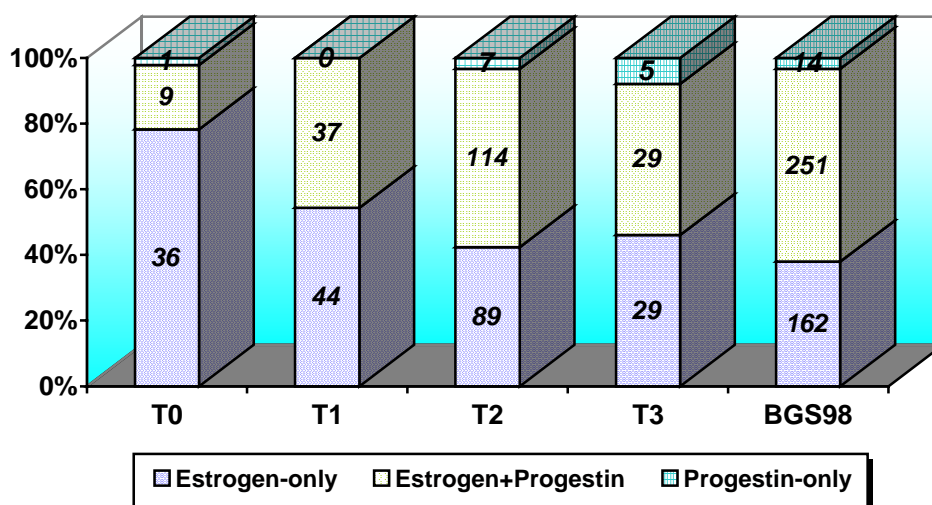
Fig 16: Profiles of HRT products used in the five German National Health Surveys from 1984 to 1999

Formulations of HRT products used in the five National Health Surveys

Unlike contraceptives, for which only oral preparations were available these days, plaster, injection and gel preparations were also used for HRT besides oral preparation. Oral preparation was still the main HRT preparation with the proportion of 83.0%. 14.5% HRT products were of the plaster-type (Fig. 17).
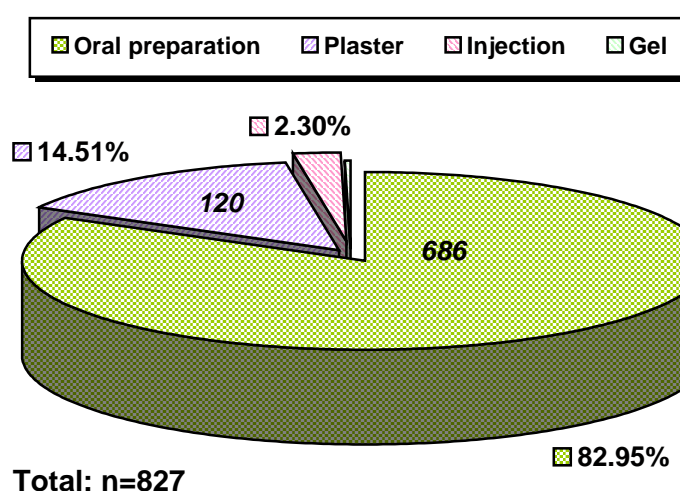

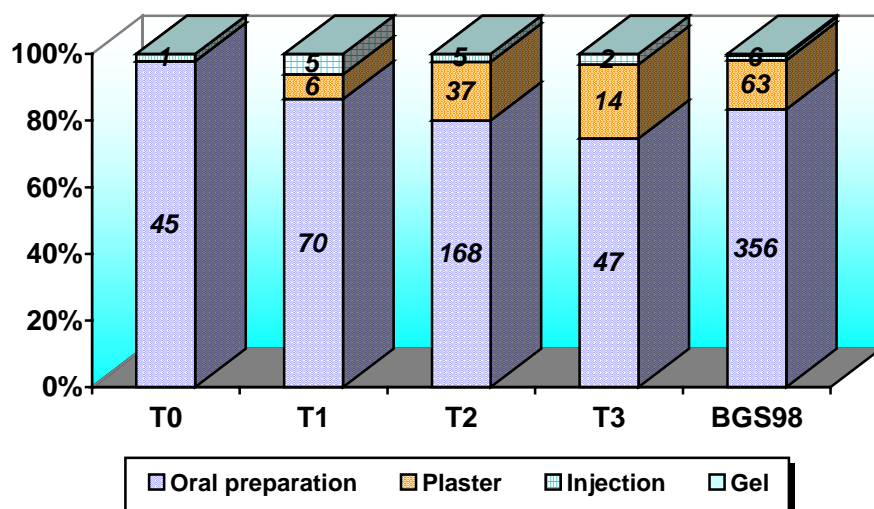**Fig. 17: Preparations of HRT products used in the five German National Health Surveys**

Fig. 18: Preparation of HRT products used in the five German National Health Surveys from 1984 to 1999

It can be seen from Fig. 18 that plaster preparation was available only after 1987 with the proportions 7.4% (6/81), 17.6% (37/210), 22.2% (14/63) and 14.8% (63/427) in survey T1, T2, T3 and BGS98, respectively.

2. Sociodemographic data and life style of steroid hormone users and controls

In addition to the data shown in last chapter 1.1 for the use rate of steroid hormones in the general population, the following chapters (2.1-2.7) show explicitly the calculations for users vs. controls.

2.1 Age

Table 14 (Page 117) shows that the average age of contraceptive users was 30-34 years in the five surveys, which is significantly less than the average of nonusers (38-41 years) in each survey (t-test, all p=0.000) as contraceptive users were mainly younger women with higher proportions in younger age groups, significantly different from that of nonusers (chi-square test, all P=0.000), whose age proportions were more similar to the total general women population of each survey as only a small part of women took OCs after all.

In contrast, the average age of HRT users was around 52-56 years old for the five surveys, significantly higher than that of nonusers in each survey (48-53 years old) (t-test, all p=0.000). HRT users concentrated on age groups of 50-59 years with much higher proportion than any other age groups. Also the age proportions of HRT users were significantly different from those of nonusers in each survey (chi-square test, all p<0.05) (Table 15, page 118).

Age is one of the most important factors that may influence health status and health-related outcomes. So it is necessary to chose age-matched controls randomly from all steroid hormone nonusers for the further comparison between users and nonusers.

2.2 Body weight and BMI

The average body weight for steroid hormone users and controls can be seen from Table 16 (Page 119) and Fig. 19. Compared with controls, steroid hormone users had, generally, a significantly lower weight especially in the earlier surveys; however, in the last survey BGS98, a difference in weight did not exist anymore between contraceptive users and controls whereas the difference enlarged between HRT users and controls.

Body mass index is calculated as weight in kilograms divided by the square of height in meter. A person is considered to be 'normal-weighted' if her BMI is not beyond
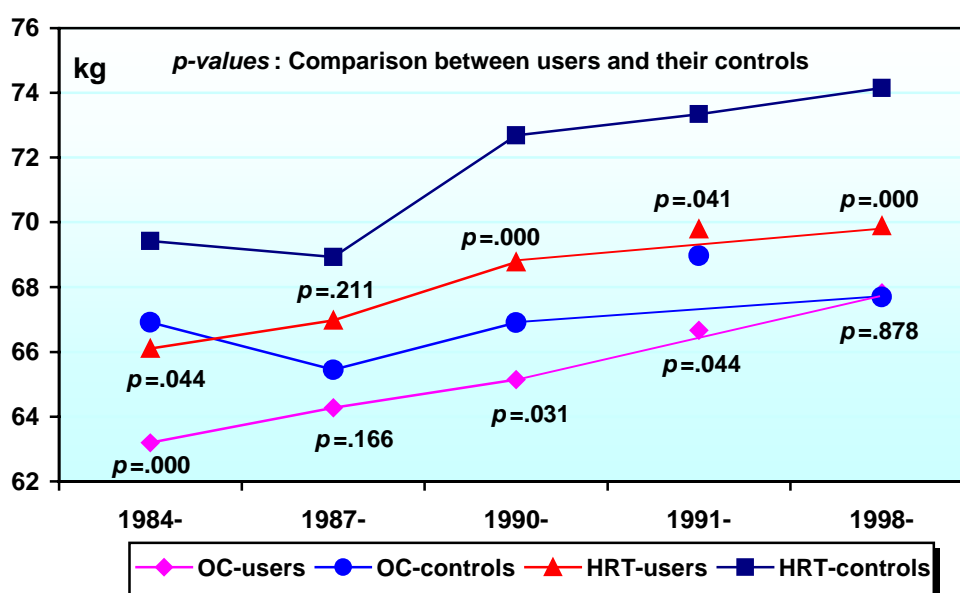

Fig. 19 : Average body weight for steroid hormone users and their controls in German women aged 25-69 years from 1984 to 1999

±10% of the average BMI, otherwise the person is considered to be 'under-weighted' (beyond -10% of average BMI) and 'over-weighted (beyond +10%).
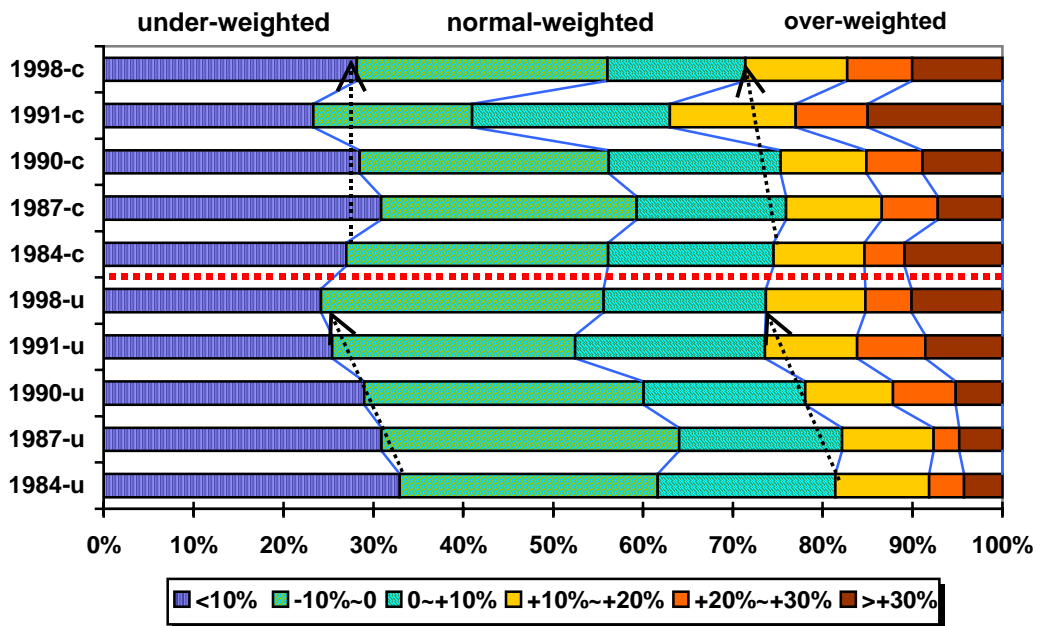

Fig. 20: BMI in contraceptive users (with 'u') and controls (with 'c') in German women population aged 25-69 years

From Table 16, it can be seen that the average BMI of contraceptive users was significantly lower than that of controls in survey T0 and survey T3. However, the
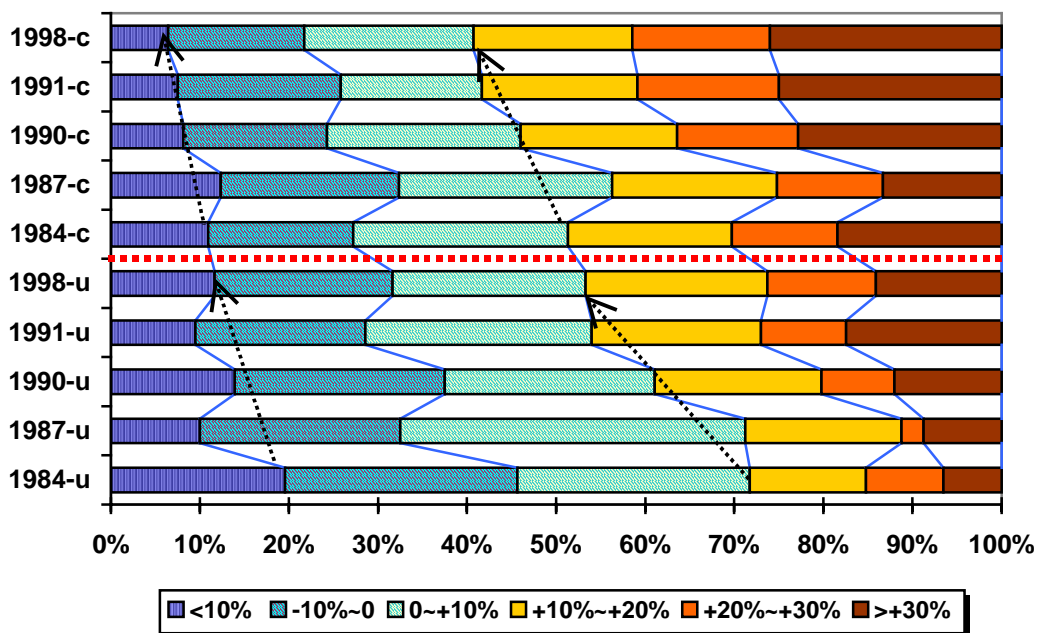

Fig. 21: BMI in HRT users (with 'u') and controls (with 'c') in German women population aged 25-69 years

proportion of over-weighted (over 10% of average BMI) in contraceptive users was less than that of controls in all five surveys. This was especially true for heavy over-weighted (over 30%) in the earlier surveys T0-T3. Fig. 20 shows the trends of BMI in contraceptive users and controls along with time from 1984 to 1998. For users there was a decreasing trend for the proportion of under-weighted and an increasing trend for over-weighted, while normal-weighted kept almost unchanged (see two parallel lines in the lower part of the figure). For nonusers, however, there were no such trends (see two parallel lines in the upper part of the figure). This was especially true for heavy over-weighted (over 30%).

The average BMI of HRT users was significantly lower than that of controls in all surveys except for survey T1 (Table 16). Unlike contraceptive users, HRT users showed the same trends for BMI as controls along with time from 1984 to 1999, namely, the proportion of under-weighted tended to decline while the over-weighted tended to increase (Fig. 21). Without exception, the proportion of over-weighted for HRT users in each survey was much lower than that of nonusers, particularly for heavy over-weighted (over +20%).

2.3 Resident places

In general there was no significant difference in the resident place for contraceptive users and controls in all surveys except for survey T2, in which the proportion of users from middle cities was higher than that of controls (Table 17). This is also to be seen from Fig. 22, contraceptive users and controls showed the same trend for the change of resident places from 1984 to 1998. However, in survey T3 there was a much higher proportion for contraceptive users and controls that came from countryside, which contrasted sharply with the other four surveys.

Comparing with controls, HRT users more often lived in large cities and less in countryside and small cities. Nevertheless, HRT users and controls demonstrated the same trend for the residence place along with time from 1984 to 1999. The proportion for large cities declined while the proportion for countryside and small cities went up both for HRT users and controls. In the survey T3 (East Germany), like the use of contraceptives, there was a much higher proportion for HRT users who came from countryside in comparison to its western counterpart (Fig. 22 and 23).
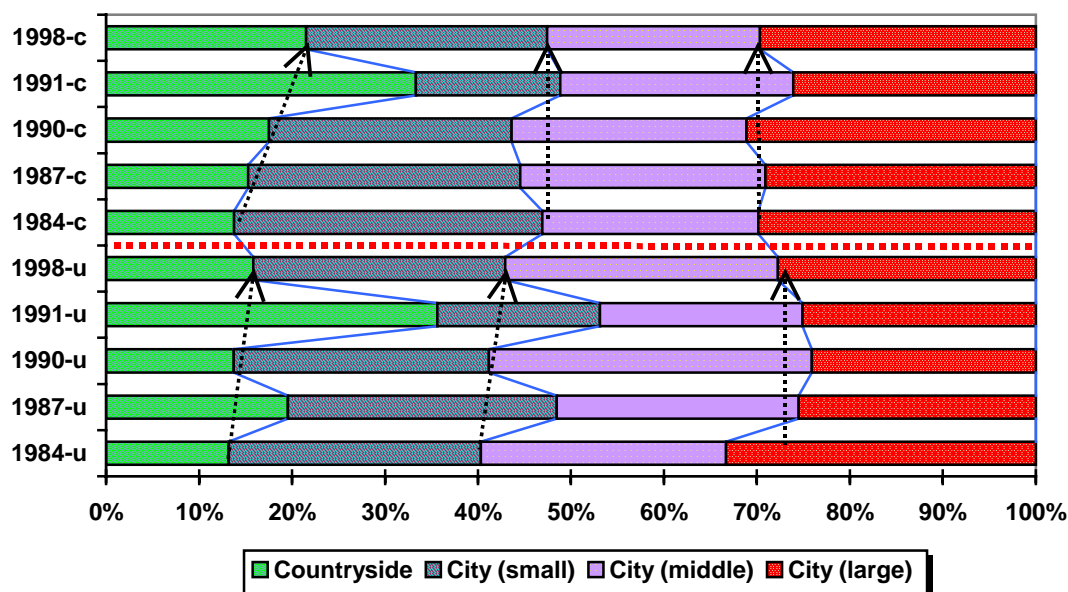
Fig. 22: Resident places for contraceptive users (with 'u') and controls (with 'c') in German women population aged 25-69 years
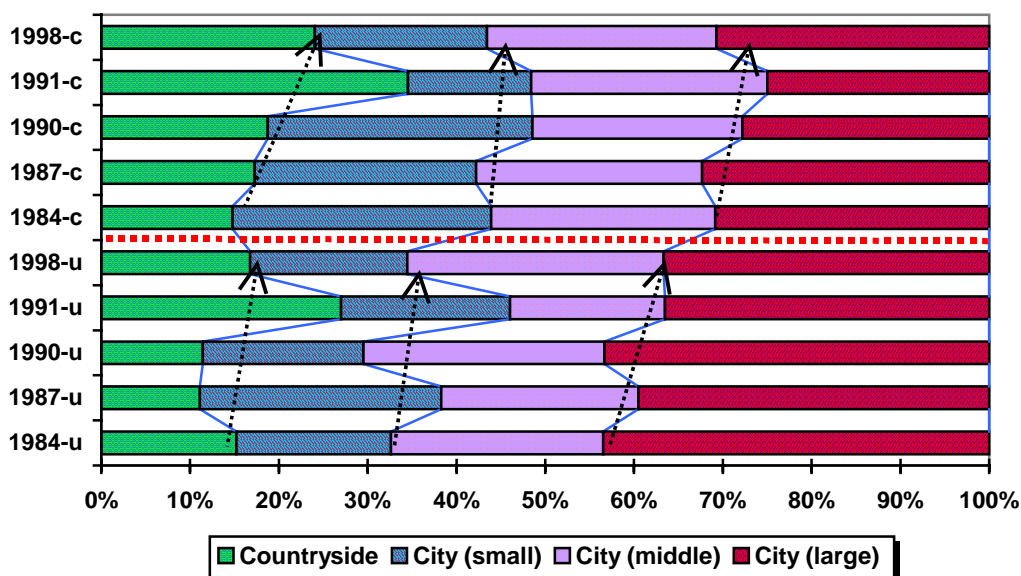

Fig. 23: Resident places for HRT users (with 'u') and controls (with 'c') in German women population aged 25-69 years

2.4 Marriage status

Table 18 showed that there was no significant difference in marriage status between controls and steroid hormone users either for contraception or for HRT. In survey BGS98, there was a higher proportion for 'single' and a less for 'married' women because the studied population in this survey, covering the young women aged 18-

25 years, was younger compared with that of the other four surveys, but also because of a continuous change in life style in the general population.

2.5 Education

According to educated years, the educational system in the former West Germany can largely be classified into primary education (including Volks- and Hauptschule, *Volks-Haupt*), middle education (Realschule, *Real-*) and higher education (including Fachhochschule and Abitur/Universität, *FH and Uni*). The 'Oberschule', existed in the former East Germany only, is comparable to and grouped into the western 'Realschule' for survey T3 and for survey BGS98, which resulted in a much higher proportion of Realschule in these two surveys (Table 19). However, there was no significant difference between OC users and controls in all surveys except for survey BGS98. For BGS98, participants who were originally from the former East Germany aged 25-69 years were sorted out separately so that they could be compared with those from the survey T3. The results were integrated into Fig. 24 and Fig. 25 together with their western counterpart. Fig. 24 shows the same trends in education for contraceptive users as the controls either in West Germany or in East Germany.

However, HRT user, both in West Germany and in East Germany, showed a higher proportion for college education (FH and Uni) and a lower proportion for primary
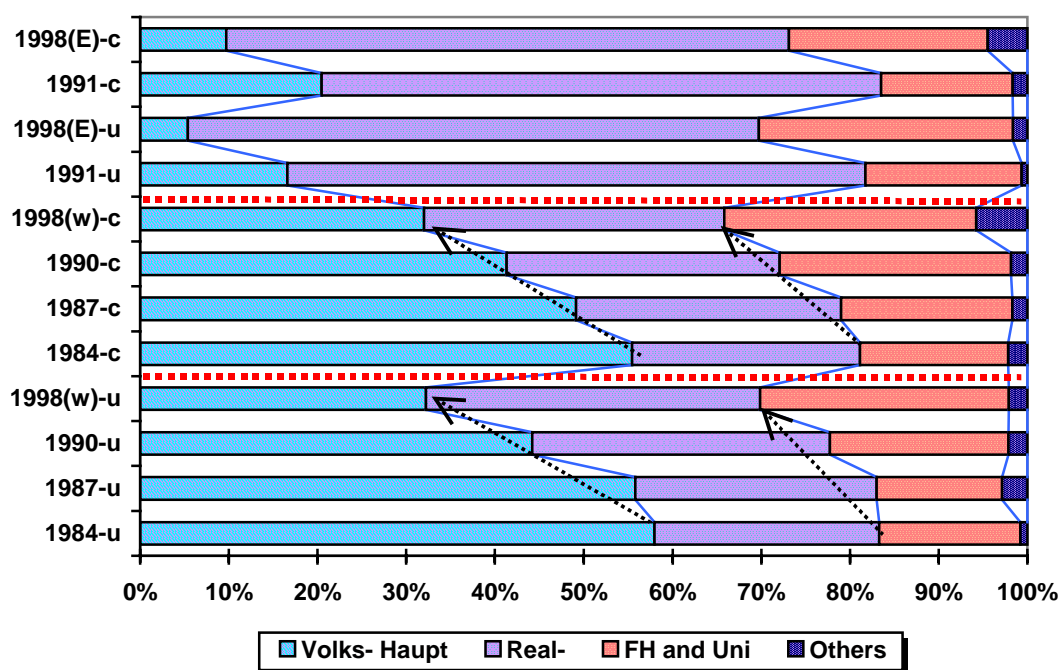

Fig. 24: Education for contraceptive users (with 'u') and controls (with 'c') in the German women population aged 25-69 years

education (Volks- Haupt) compared with their controls; the number of college-educated HRT users increased from 1984 to 1999 (Fig. 25 and Table 19).
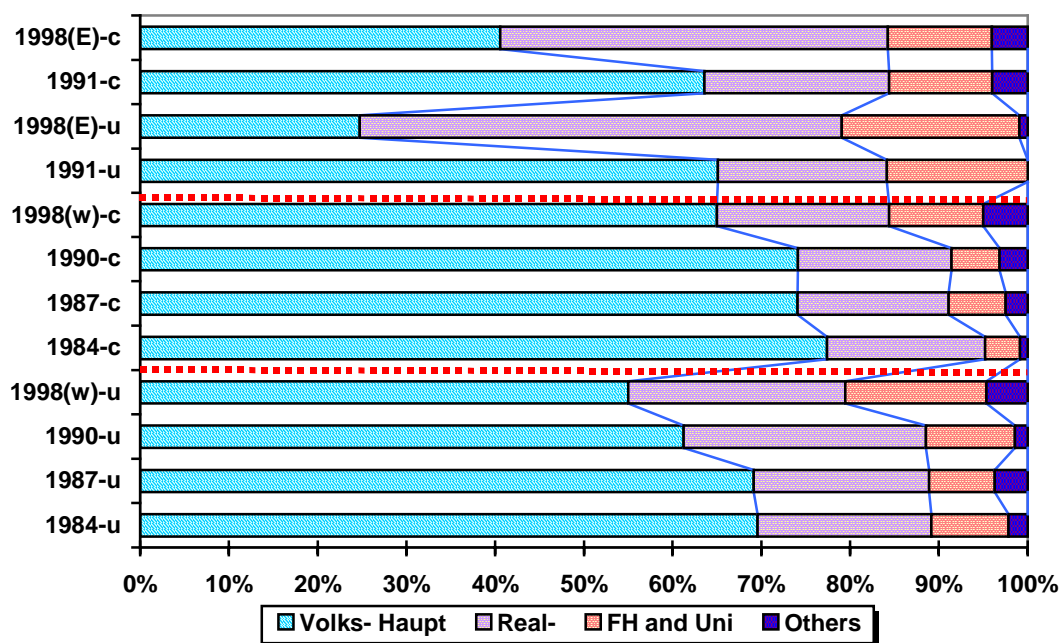

**Fig. 25: Education for HRT users (with 'u') and controls (with 'c')
in the German women population aged 25-69 years**

2.6 Social class

From 1984 to 1999, contraceptive users showed the same profiles as controls regarding social class, and the proportion of the three social classes in each survey changed very little except that the proportion of upper social class was higher for
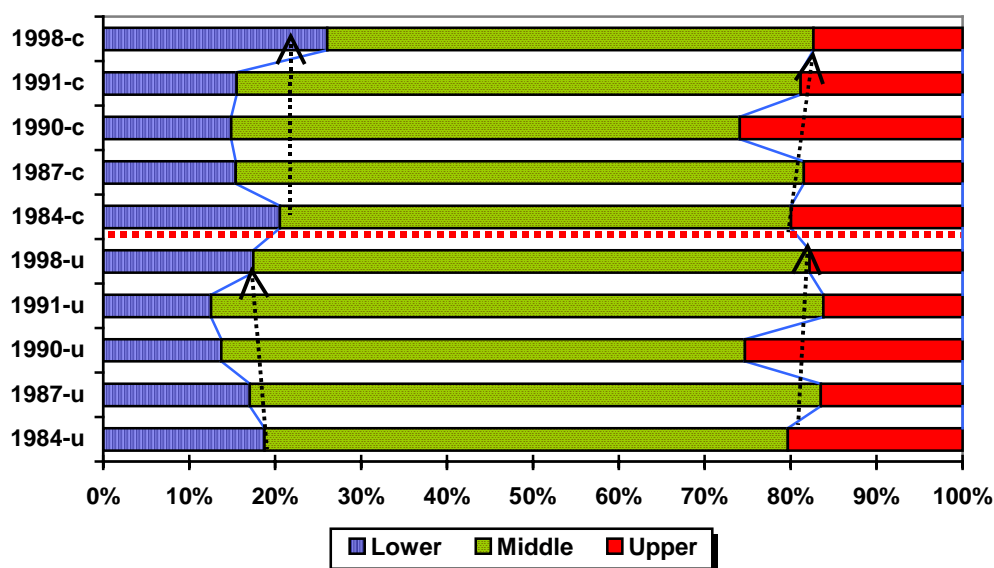

**Fig. 26: Social class for contraceptive users (with 'u') and controls
(with 'c') in German women population aged 25-69 years**

contraceptive users in survey T2 (1990-u) in relation to the other four surveys.

This was also observed for their controls (1990-c) in the same survey (Fig. 26). There was no significant difference between contraceptive users and controls in the proportion of different social classes in all surveys except for BGS98, in which the proportion was low in lower social class while high in middle class. (Table 20).
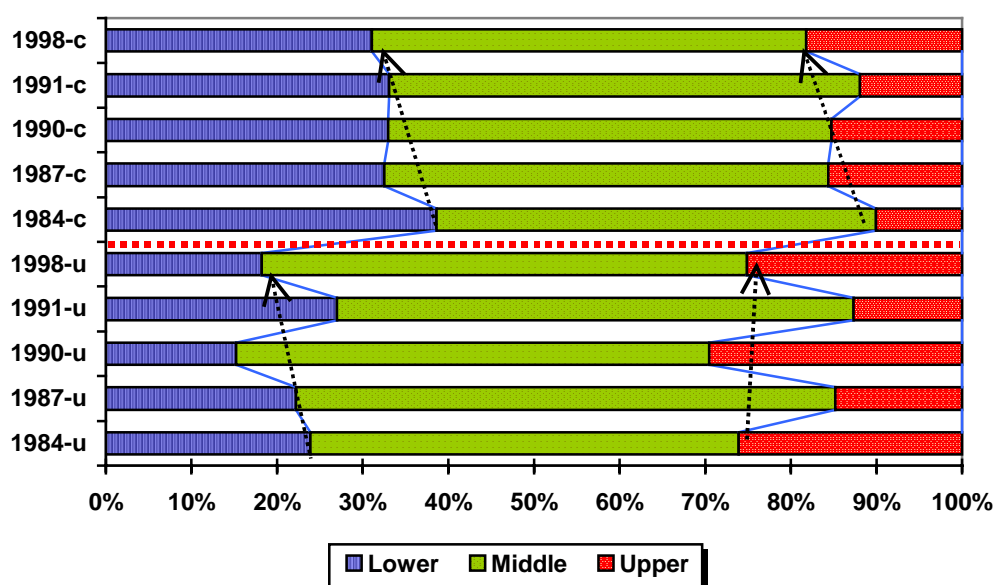

**Fig. 27: Social class for HRT users (with 'u') and controls (with 'c')
in German women population aged 25-69 years**

However, Fig. 27 shows a clear association for the use of HRT and social class. Comparing with that of controls in each survey, the proportion of lower social class was significantly lower while the proportion of upper social class was higher in HRT users, this was especially true for the surveys T0, T2 and BGS98 with a relative large sample size of HRT users.

2.7 Smoking status

In earlier surveys of T0 and T1, a significant difference was found between contraceptive users and controls with regarding to smoking status (Table 21). There were more smokers and less nonsmokers in contraceptive users compared with controls. In the later surveys T2, T3 and BGS98, however, such a difference existed no longer (Table 21 and Fig. 28). From 1984 to 1999, among contraceptive users there were more and more nonsmokers while number of smokers decreased. Such changes were not found in controls. In fact, the frequency of smokers among controls

tended to increase from 1984 to 1999. This reflects the awareness of an increased risk of cancers under complications in smokers when receiving oral contraception.
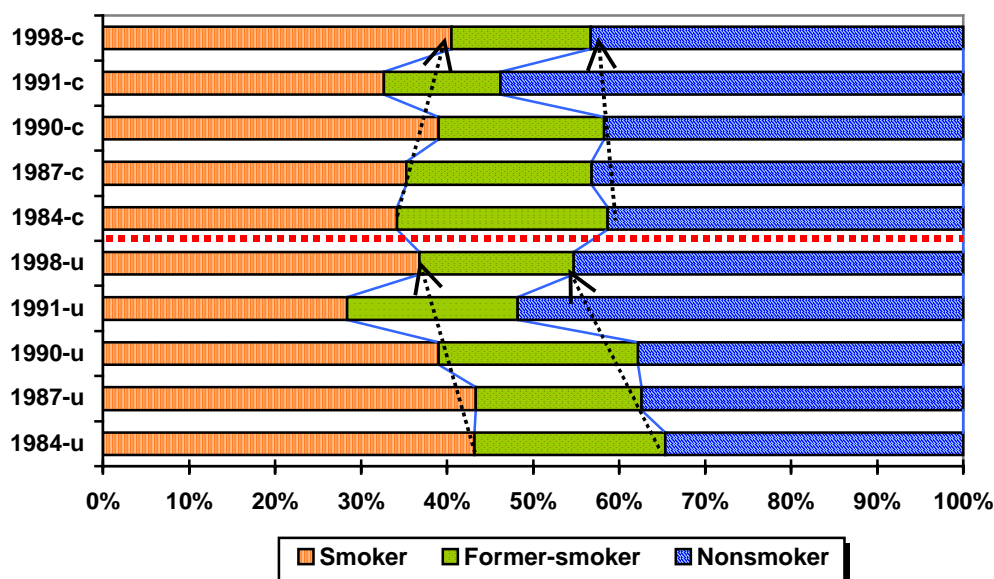
Fig. 28: Smoking status for contraceptive users (with 'u') and controls (with 'c') in German women population aged 25-69 years

From Table 21 and Fig. 29, there were much more former smokers among HRT users in each survey compared with controls, particularly for the first three surveys. Both for HRT users and controls, there were no substantial changes for nonsmokers in each survey along with time from 1984 to 1999; but it seems there was an increase trend for smokers among HRT users whereas such trend did not exist among controls.
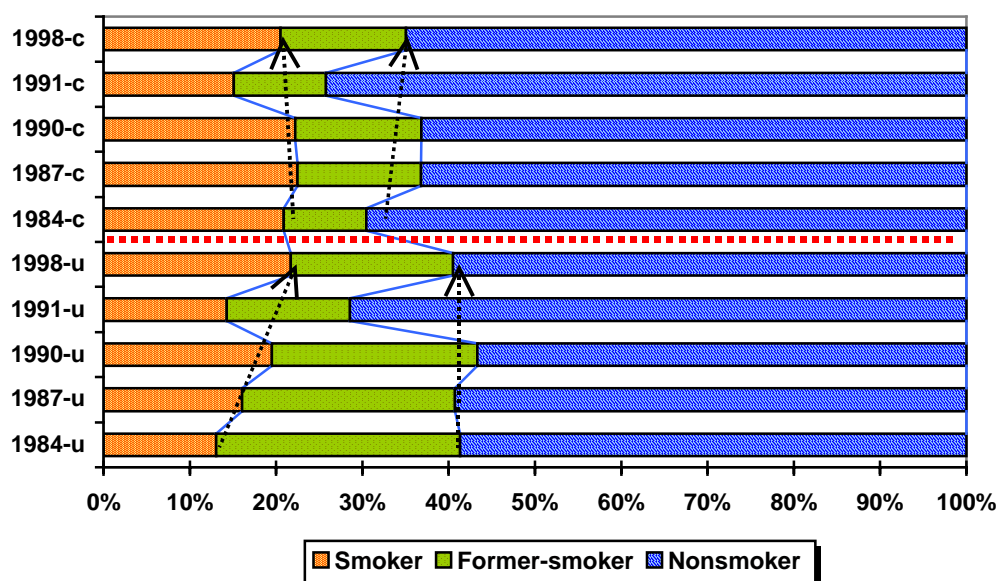
Fig. 29: Smoking status for HRT users (with 'u') and controls (with 'c') in German women population aged 25-69 years

3. Health and diseases of steroid hormone users and controls

3.1 Self-assessed health status

For the question 'How do you think of your current health status? (Wie würden Sie Ihren gegenwärtigen Gesundheitszustand beschreiben?), Table 22 shows the results of the question for steroid hormone users and controls. Generally there were no significant differences between steroid hormone users and controls regarding to self-assessed health status except for HRT users in survey T3 (GDR-survey), whose average score for health status was significantly higher than that of their controls (suggesting a worse health status). The average score of contraceptive users tended to be lower than that of controls in each survey, suggesting a better health status; while the average score of HRT users tended to be higher than their controls, suggesting a worse health status. The profile of proportion percent of health status in survey BGS98 was different greatly from that of other four surveys because the choices provided in the questionnaire for survey BGS98 differed from those for the other four surveys. 5 choices in former were: 1. Ausgezeichnet (excellent), 2. Sehr gut (very good), 3. Gut (good), 4. Weniger gut (not so good), 5. Schlecht (bad), while in latter: 1. Sehr gut (very good), 2. Gut (good), 3. Zufriendenstellend (satisfied), 4. Weniger gut (not so good), 5. Schlecht (bad). As a usual, 'Gut' was often chosen by most subjects who were under ambulant care.

3.2 Health-related satisfaction with life and the results of SF-36 for survey BGS98

Seven aspects were designed for the measuring of satisfaction with life: job, residence, financial situation, recreation, health, family situation and relationship to friends, neighbors and acquaintances etc. The overall satisfaction with current personal life was also measured (Table 23). Each item was scored from 1 (very unsatisfied) to 7 (very satisfied). In survey BGS98, contraceptive users were more satisfied whereas HRT users were not so satisfied with their job when compared with their controls. Fig. 30 shows the average score of satisfaction with overall life for women aged 25-69 years in the western part of Germany only. Compared with controls, contraceptive users tended to have a higher whereas HRT users tended to have a lower score of satisfaction with life. In the last ten years HRT users had a dramatic decline for their satisfaction with life (Fig. 30). Although there was no significant difference for the overall satisfaction with life between steroid hormone
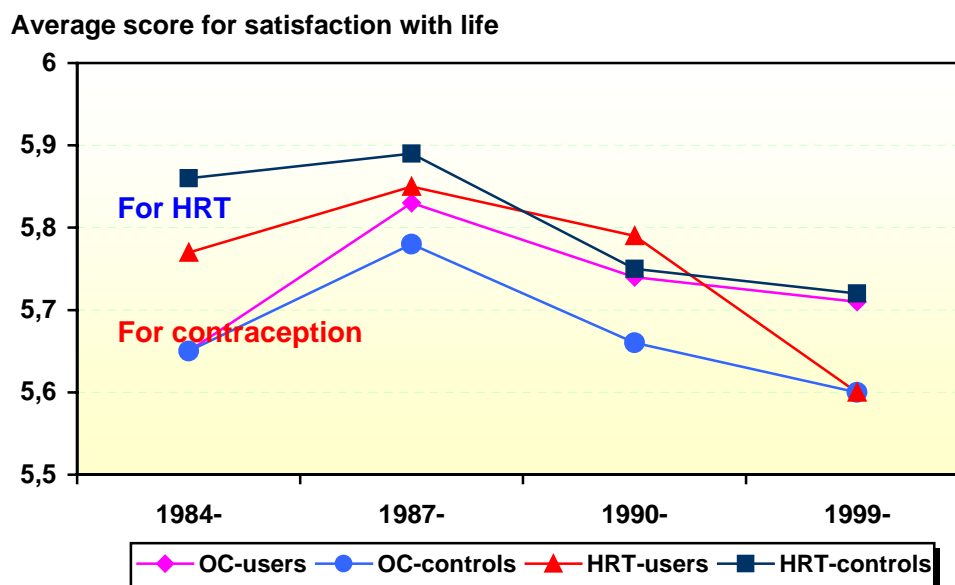
Average score for satisfaction with life

Fig. 30: Average scores of satisfaction with overall life for steroid hormone users and controls in the western German women population aged 25-69 years

users and control, the average score for satisfaction with health tended to be higher in contraceptive users whereas tended to be lower in HRT users compared with that of their controls (Fig. 31). From 1990 to 1999, the difference for satisfaction with health was significantly enlarged between steroid hormone users and control in women population aged 25-69 years (Fig. 31).
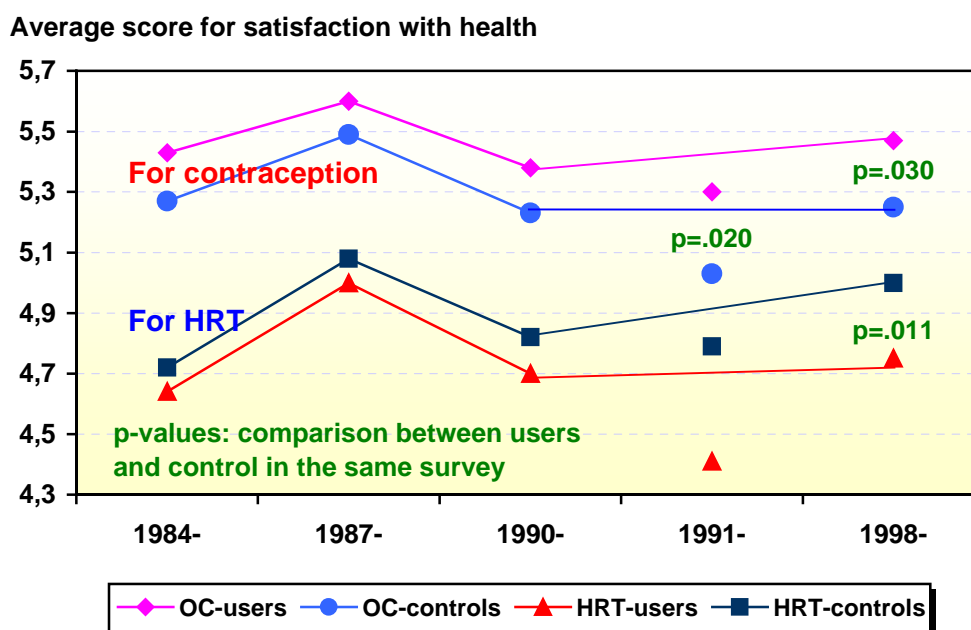
Average score for satisfaction with health

Fig. 31: Average scores of satisfaction with health for steroid hormone users and controls in the German women population aged 25-69

The SF-36 is a general instrument widely used for the measuring of health-status, which includes eight health concepts: physical function, role limitation due to physical problems, body pain, general health perception, energy/vitality, social function, role limitations due to emotional problems and mental health. For each dimension, item scores are coded, summed and transformed on to a scale from 0 (worst possible health state) to 100 (best possible health state) [101]. Compared with controls, contraceptive users had a significantly higher score on physical functioning, role limitation due to physical problems and general health; as for the other 5 items, contraceptive users had, though, a higher score, but it was statistically not significant. Contrary to contraceptive users, HRT users tended to have a lower score in the eight health concepts, of which the scores in body pain and in vitality/energy were significantly lower (Table 24). The results of SF-36 for survey BGS98 were in line with those shown in Table 23.

3.3 Histories of some diseases in the past 12 months

Fig. 32-47 show some disease histories in the past 12 months (including those who had suffered before and those current sufferers) for steroid hormone users and controls aged 25-69 years from 1984 to 1998.
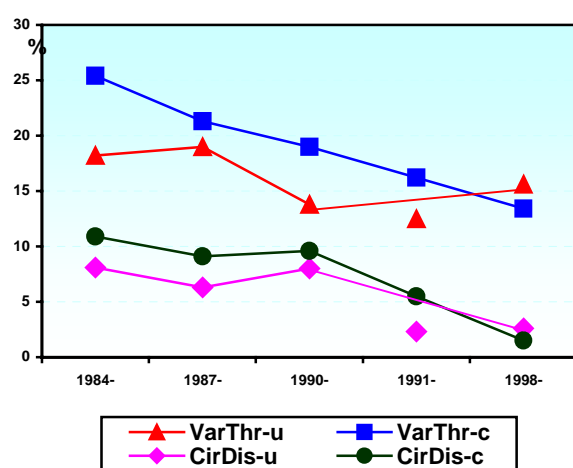

Fig. 32: History of varicosity and thrombosis (VarThr) and circulation disorders in legs (CirDis) in contraceptive users and controls aged 25-69
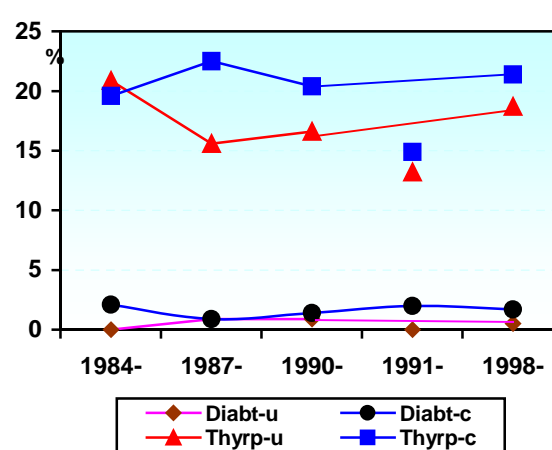

Fig. 33: History of thyropathy (Thyrp) and diabetes (Diabt) in contraceptive users and controls aged 25-69
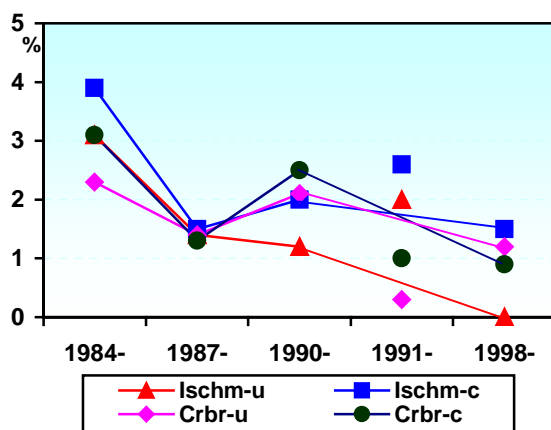
Fig. 34: History of ischemia myocardial (Ischm) and cerebral circulation disorders (Crbr) in contraceptive users and controls aged 25-69
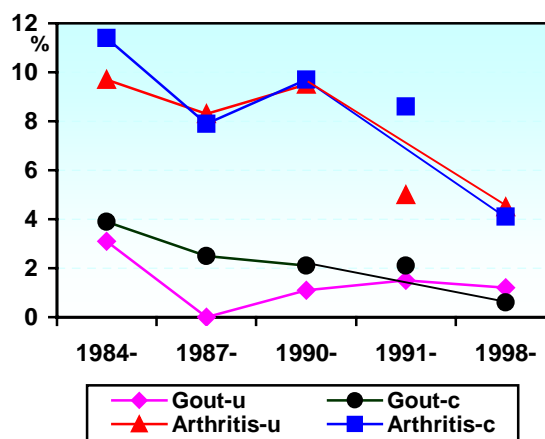
Fig. 35: History of gout and lithemia (Gout) and arthritis (Arthritis) in contraceptive users and controls aged 25-69
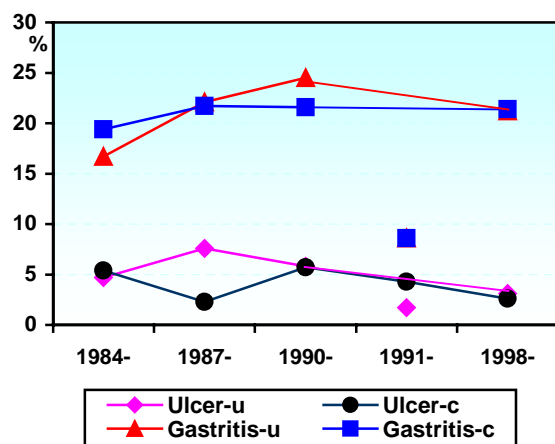
Fig. 36: History of ulcer(gastric and duodenal) and gastritis in contraceptive users and controls aged 25-69
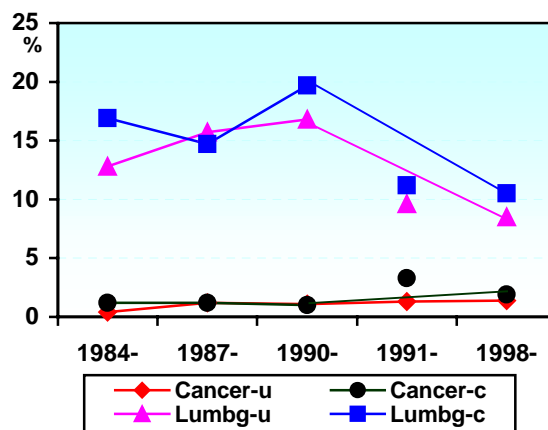
Fig. 37: History of cancer(Cancer) and lumbago (Lumbg) in contraceptive users and controls aged 25-69
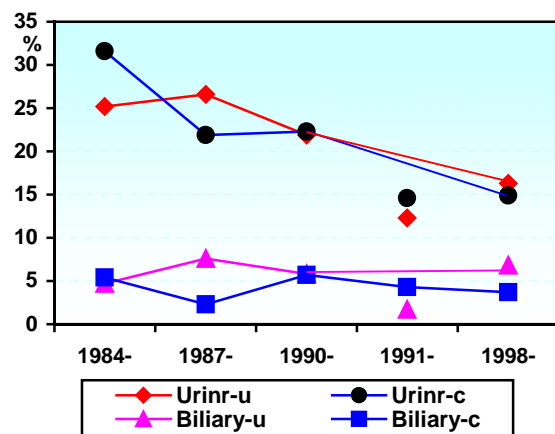
Fig. 38: History of urinary diseases (Urinr) and biliary diseases (Biliary) in contraceptive users and controls aged 25-69
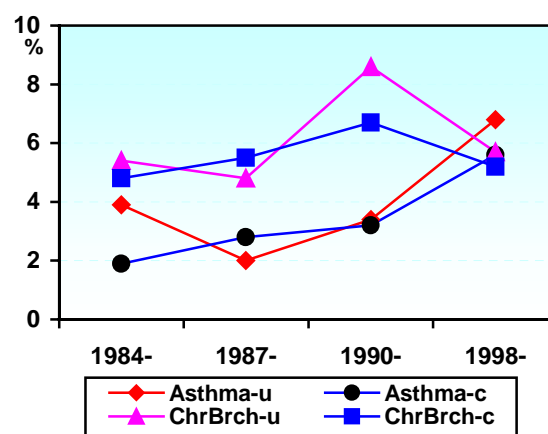
Fig. 39: History of asthma (Asthma) and chronic bronchitis (ChrBrch) in contraceptive users and controls aged 25-69

These diseases were self-reported and should be confirmed by interviewing physicians. For most diseases listed, no significant differences were found between contraceptive users and controls in each survey though contraceptive users tended to have a lower prevalence rate of disease histories, particularly for diseases like vascular diseases (varicosity, thrombosis and other circulation disorders in lower limbs, Fig. 32). This reflects the relative contraindications for OC prescription. Moreover, myocardial ischemia and cerebral circulation disorders (Fig. 34), endocrine diseases like diabetes and thyropathy (Fig. 33), gout and lithemia (Fig. 35) were less often reported by OC users, though not all these differences in disease histories were statistically significant (Table 25). For most diseases/symptoms, contraceptive users and controls showed similar trends from 1984 to 1998.
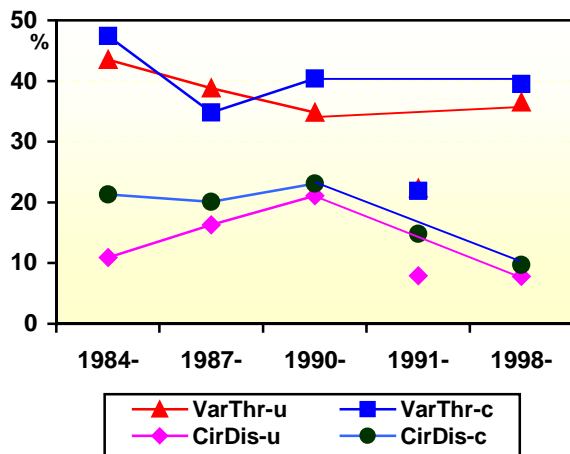
Fig. 40: History of varicosity and thrombosis (VarThr) and circulation disorders in legs (CirDis) in HRT users and controls aged 25-69

Fig. 41: History of thyropathy (Thyrp) and diabetes (Diabt) in HRT users and controls aged 25-69

Fig. 42: History of ischemia myocardial (Ischm) and cerebral circulation disorders (Crbr) in HRT users and controls aged 25-69
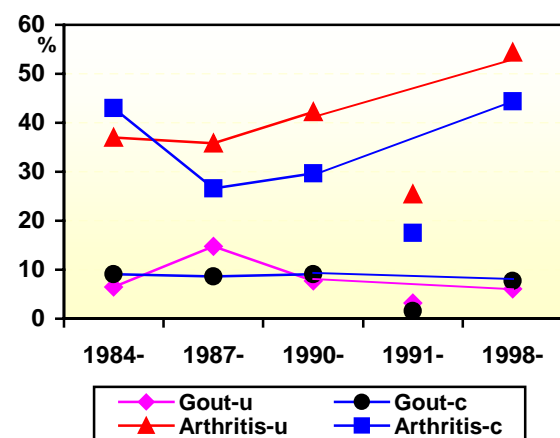
Fig. 43: History of gout and lithemia (Gout) and arthritis (Arthritis) in HRT users and controls aged 25-69
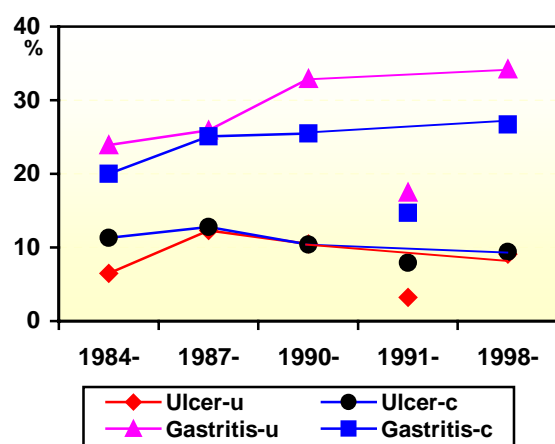
Fig. 44: History of ulcer(gastric and duodenal) and gastritis in HRT users and controls aged 25-69
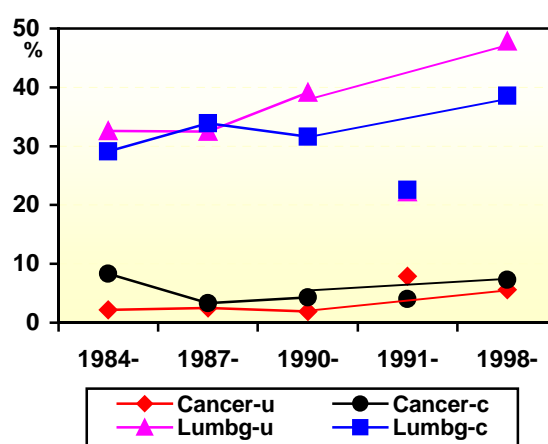
Fig. 45: History of cancer(Cancer) and lumbago (Lumbg) in HRT users and controls aged 25-69

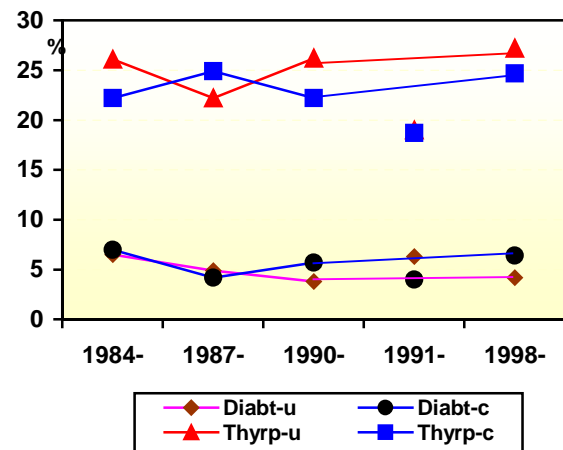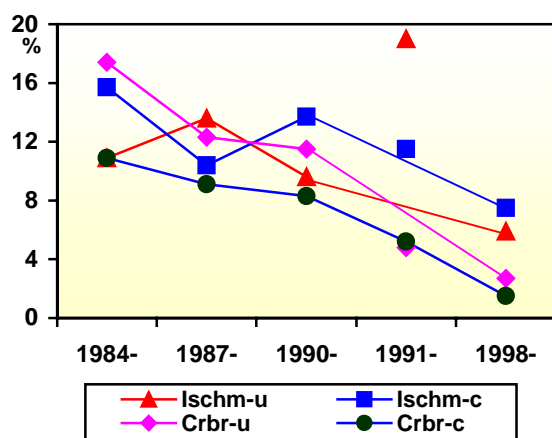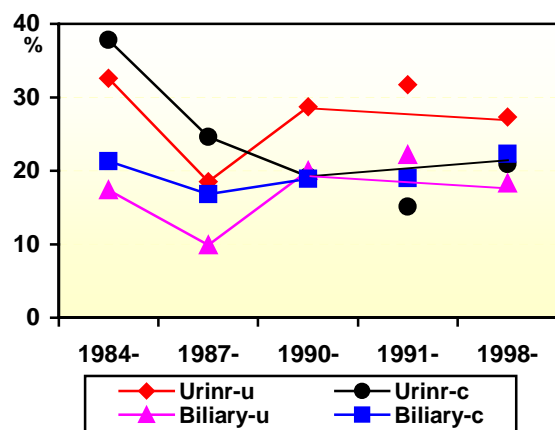**Fig. 46: History of urinary diseases (Urinr) and biliary diseases (Biliary) in HRT users and controls aged 25-69**
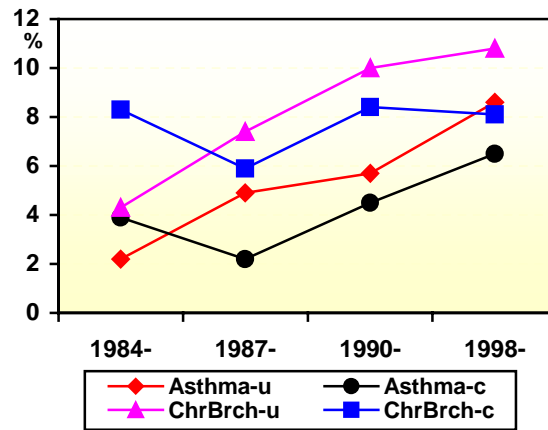
Fig. 47: History of asthma (Asthma) and chronic bronchitis (ChrBrch) in HRT users and controls aged 25-69

Fig. 40-47 show the disease histories for HRT users and controls from 1984 to 1998. Unlike contraceptive users, HRT users had a different profile of disease histories in comparison to their controls. Generally, HRT users and controls showed similar trends in disease history from 1984 to 1998 and no significant differences in disease histories could be found between HRT users and controls in each single survey. This holds true for cardiovascular diseases (myocardial ischemia, varicosity and thrombosis, cerebral circulation disorders, circulation disorders in lower limbs), endocrine diseases (diabetes and thyropathy), ulcer diseases (gastric and duodenal), biliary diseases (cholecystitis and gallstones) and cancers. Disease history for myocardial infarction and stroke was low both in HRT users and controls. However,

for respiratory diseases (asthma and chronic bronchitis), urinary diseases (cystic calculus, cystourethritis and nephritis), lumbago and sciatica, gastritis, arthritis and allergic diseases other than hay fever, HRT users showed a higher prevalence than controls. This can be seen from Table 26, though not all differences were statistically significant in each single survey (Table 26).

Other disease histories for contraceptive users and controls in survey BGS98 only
Table 27 shows diseases histories for steroid hormone users and controls from survey BGS98 only. These data were not covered in Table 25 and Table 26. Compared with controls, contraceptive users had a significantly lower history in hypoferric anemia, epilepsy, meningitis, mental disorders and addictive disorders whereas HRT users had a significantly higher history in osteoporosis, migraine, mental disorders and disorders in uterus, ovaries and oviducts.

3.4 Prevalence of diseases/symptoms
3.4.1 Unspecific diseases/symptoms
The prevalence of unspecific diseases/symptoms listed in Table 28 and Table 29 was very high particularly for HRT users and controls because these diseases/symptoms were very common and occurred often in healthy individuals, too. For most of them, no significant differences were found between steroid hormone users and controls and no apparent trends could be found from 1984 to 1999. For all diseases/symptoms found with significant differences in Table 28 and Table 29, contraceptive users had a lower prevalence rate (lump feeling in the throat, feeling of weakness, swallowing difficulty, nausea, irritability and oversensitivity, lumbago and backache, feeling of heaviness and weakness in legs and tremble) whereas HRT users had a higher prevalence rate (stitch, torsion spasm or pain in chest, subjective feeling of unrest) than their controls. Obviously, HRT users suffered more languor and fatigue, dizziness and vertigo, and more pains on back, neck and scapula than controls in all surveys. The prevalence of unspecific diseases/symptoms of steroid hormone users reflected their self-assessed health status in comparison with controls.

3.4.2 Specific diseases/symptoms, menstrual cycles and child-bearing

Menstrual cycle (Table 30)

Quite naturally, significantly more contraceptive users had menstrual cycles than controls in all five surveys. Moreover, women who still had menstrual cycles, more contraceptive users had regular cycles than their controls (in T1 and BGS98, p<.05 and in T2, p=.084). From 1984 to 1999, increasingly more women who still had menstrual cycles took HRT; in survey BGS98, significantly more HRT users (32%) had menstrual cycles than controls (21.4%).

From the data of survey BGS98, the age at menarche differed between contraceptive users and controls, contraceptive users had a later age at menarche (13.33 *vs.* 13.09 years, *p*<0.05). For HRT users there was no such difference (13.7 vs. 13.6, p>0.05), while HRT users were younger for the age at menopause than nonusers (46.3 vs. 47.4, p<0.05) (Table 30). A lack of exposure to large endogenous estrogen (e.g. pregnancy) might be a predictor for HRT use. Therefore, the association of HRT use and number of pregnancies was next investigated.

Number of term pregnancies and age at first term pregnancy (Table 31)

Table 31 lists the data for survey T0-T3 only. There was no significant difference to be found between contraceptive users and controls in the average number of term pregnancies and in the average age at first pregnancy. Nevertheless, contraceptive users tended to have 1-2 children; in surveys T2 and T3, less contraceptive users had children over 3 compared with their controls. Compared with women in eastern Germany, women in western Germany had less children and were two years older on average at their first delivery.

Compared with controls, HRT users had less term pregnancies on average (1.78 vs. 2.02, p=0.003) in the first three surveys and were less likely to have more than 3 children especially in survey T0 and T3 (both p<0.05). No difference was found for HRT users and controls in the age at first pregnancy except for survey T1. As with contraceptive users, HRT women in western Germany were two years older at their first delivery on average.

Blood pressure and hypertension (Table 32)

Blood pressure was measured of 2-3 measurements when women were at rest during the medical interview, the mean was adopted. The first and fifth Korotkoff sounds were recorded for the systolic and diastolic blood pressure, respectively. In Table 32, women were categorized as hypertensive if: 1) they were current user of anti-hypertension medications (self-reported); 2) they had a systolic blood pressure (SBP) of 140 mm Hg or higher; 3) they had a diastolic blood pressure (DBP) of 90 mm Hg or higher.
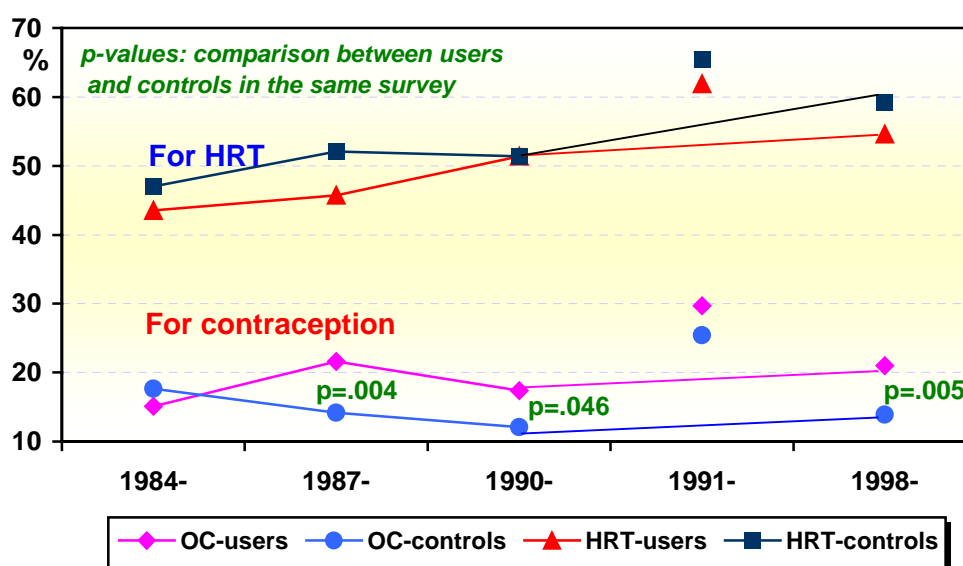
Fig. 48: Prevalence of hypertension for steroid hormone users and controls from 1984 to 1999 in the German women population aged 25-69

From Table 32 and Fig. 48, contraceptive users had a significantly higher prevalence rate of hypertension and a significantly higher average SBP than that of controls in surveys T1, T2 and BGS98. From 1984 to 1999, on women aged 25-69 years, the average SBP increased from 121.6±14.2 to 125.5±16.0 mm Hg in contraceptive users while changed very little in controls (121.6±16.2 to 120.7±14.2 mm Hg, SBP data for 1999 were not listed in the table). There was no significant difference in the use of anti-hypertension medications between contraceptive users and controls in all surveys, however.

Between HRT users and controls, no significant differences could be found for the prevalence of hypertension as well as for the average SBP in the first four surveys. Survey BGS98 showed different profiles in blood pressure from the other surveys because it covered participants aged 70-79 years. For women under 70 years of age, results of survey BGS98 were consistent with other four surveys regarding the prevalence of hypertension (54.6% vs. 59.2%, p=.122) (Fig. 48), the percentage of antihypertensive therapy (23.4% vs. 25.9%, p=.343) as well as the average SBP (141.9±21.6 vs. 143.0±21.9, p=.417).

Fasting blood glucose and diabetes (Table 33)

In Table 33 diabetes was defined as fasting glucose concentration in serum >=7 mmol/L. Moreover women currently undergoing anti-diabetic therapy were defined as diabetics. There was no significant difference for the prevalence of diabetes between contraceptive users and controls in all five surveys; and the mean fastig glucose level of contraceptive users was very close that of controls in each survey (Fig. 49). The same was true for the percentage of women on anti-diabetic therapy.

Compared with controls, HRT users had an apparent lower fasting glucose level in women population aged 25-69 (Fig. 49), particularly in surveys T2 and BGS98, in which the difference was statistically significant both in the prevalence of diabetes
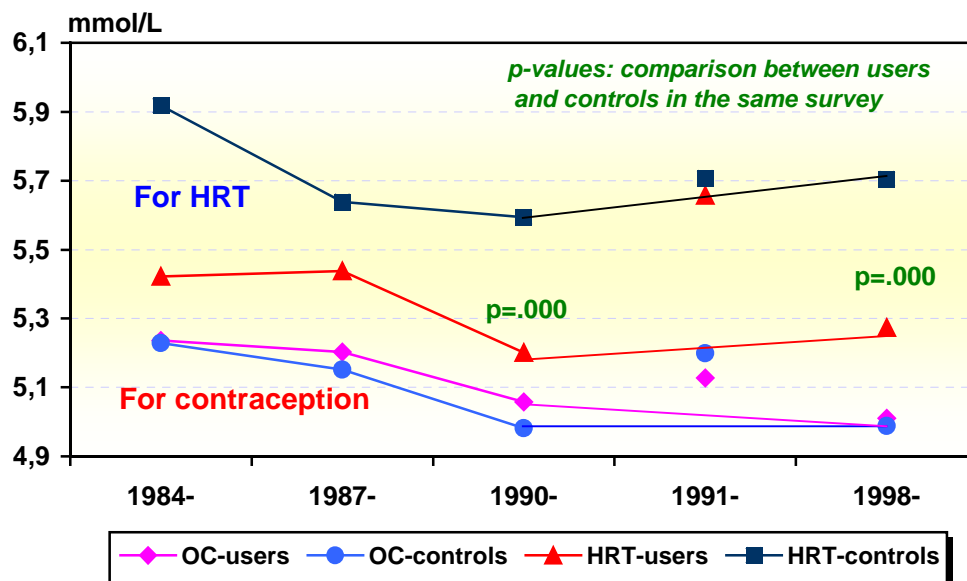
Fig. 49: Fasting glucose concentration in serum for steroid hormone users and controls from 1984 to 1999 in the German women population aged 25-69

and in the average glucose concentration (Table 33). Further, less HRT users took anti-diabetic medications in BGS98.

Blood uric acid and hyperuricemia (Table 34)

Higher concentration of uric acid in serum (hyperuricemia, >=357 μmol/L) results in gout. From Table 34, no difference was found between contraceptive users and controls in all surveys regarding to the prevalence of hyperuricemia and average uric acid concentration. The same was true for HRT users and controls in all surveys except for BGS98, though HRT users tended to have a lower uric acid concentration.

Blood lipids and hyperlipidemia (Table 35)

Hyperlipidemia, covering hypercholesteremia, hypertriglyceridemia or the both, was defined as total cholesterol concentration >=5.2 mmol/L or triglycerides concentration >=1.7 mmol/L [102] or those undergoing lipid-lowering therapy. Blood lipids were measured in the study population fasting for at least 3 hours and with no alcohol consumption for 24 hours. Therefore, the number of women considered to be

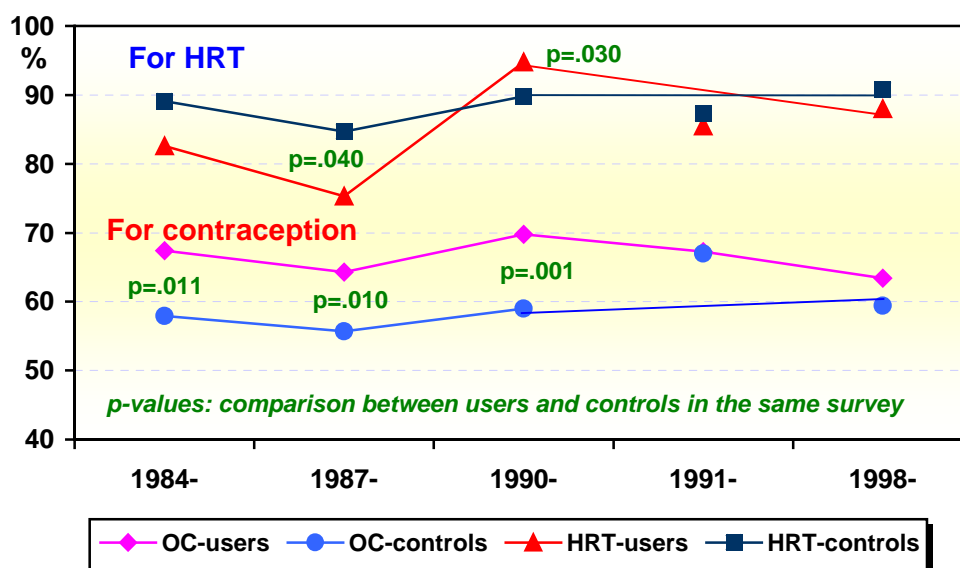**Fig. 50: Prevalence of hyperlipidemia for steroid hormone users
and controls from 1984 to 1999 in the German women population
aged 25-69**

hyperlipidemic could be an overestimation and depends on the chosen limits/cut-off points in the literature. Yet, an influence of hormone intake should become obvious

nevertheless. Except for survey T3, the other surveys showed consistently that contraceptive users had a higher prevalence rate of hyperlipidemia and a significantly higher level of triglycerides compared with controls (Table 35). No difference was found between contraceptive users and controls in the ratio of HDL-C/Ttl-C in all surveys except for BGS98 though the total cholesterol and HDL-cholesterol levels of users were significantly higher in surveys T2 and BGS98.

In contrast to contraceptive users, the mean triglycerides concentrations of HRT users did not exceed (even significantly lower in BGS98) those of controls, and the total cholesterol concentrations tended to be lower with statistical significance in surveys T1-2 and BGS98, whereas HDL-C concentrations tended to be higher with statistical significance in surveys T0 and BGS98 compared with those of controls (Table 35). In particular, the mean LDL-C concentration was significantly lower while the ratio of HDL-C/Ttl-C was significantly higher than that of controls in all surveys except for T3. However, there was no significant difference for lipid-lowering therapy between steroid hormone users and controls in all surveys.

4. Utilization of health services and co-medications of steroid hormone users and controls

4.1 Utilization of health services

Number of clinical contacts ('visiting a doctor') in the last 4 weeks

Table 36 shows the percentage of the visiting of a specific doctor in the last 4 weeks for every 100 steroid hormone users or controls. Both steroid hormone users and controls visited more often general practitioners, internists, gynecologists than any other specialists. There was no significant difference to be found between contraceptive users and controls with respect to clinical contact in the last 4 weeks. In contrast, obviously more HRT users than their controls visited internists and gynecologists in the last 4 weeks, particularly in the first three surveys.

Hospitalization in the last 12 months

More controls than contraceptive users had been hospitalized in the last 12 months, partly due to a hospital-based parturition. For those who had been hospitalized, contraceptive users tended to have a shorter stay in hospitals than controls. The proportion of hospitalization for HRT users was close to that for their controls in all

surveys except for T3, in which significantly more HRT users had been hospitalized. However, there was no significant difference in the average days of hospitalization to be found between HRT users and controls in all five surveys (Table 37).

4.2 Co-medication in the last 7 days

Table 38 and Table 39 list all drug uses in the last 7 days for steroid hormone users and their controls. Apart from the category G00 (agents used in genito-urinary system and sex hormones used for contraception and HRT), contraceptive users, overall, used less medications particularly in categories A00 (mainly A11 vitamins and A12 mineral supplements) and B00 (agents used for blood and blood forming organs), but a little more analgesics (N02) (most often OTC drugs containing acetylsalicylic acid, paracetamol with or without caffeine, and anti-migraine preparations) than controls in all five surveys (Table 38). Notably, co-medications like broad-spectrum antibacterials (J00) may reduce the effectiveness of OCs because of the destroying of normal bacterial flora in the intestine that can help estrogens to be reabsorbed via enterohepatic circulation, and co-medication with cytochrome-P450-enzyme inductor like rifampin and barbiturates will accelerate the metabolism of estrogens and progestogens, leading to decrease of contraceptive effectiveness. An OTC herbal product, St. John's Wort, commonly used for depression, may decrease the effectiveness of OCs, too.

Though medications were very close to controls in all surveys except for BGS98, HRT users tended to use psycholeptics (N05, including hypnotics and sedatives), psychoanaleptics (N06, for example antidepressants), as well as non-therapeutic medications such as vitamins (A11) and mineral supplements (A12) and tonics (A13) more often than controls. For agents used in cardiovascular system (C00), no difference could be found between HRT users and controls, however (Table 39).

5. Laboratory parameters of steroid hormone users and controls

Blood concentrations of fasting glucose, uric acid and lipids are listed in Tables 33, 34 and 35, respectively. From Table 40, most surveys revealed that contraceptive users had significantly higher levels of ferric ions (Fe), ferritin and transferrin, corresponding to less blood loss during menstruation, but significantly lower concentrations of inorganic phosphate, calcium (2.333 vs. 2.347 mmol/L, p=0.037, for

users and controls aged 25-69 in survey BGS98, data not shown), albumin, bilirubin, cholinesterase. Significant differences between users and controls existed for red blood cells count (RBC), haemoglobin, thiocyanate, blood urea nitrogen (BUN) in survey T3, which differed from the other surveys.

In most surveys concentrations of inorganic phosphate, γ-GT, cholinesterase, albumin and RBC were significantly lower in HRT users than those in controls (Table 41). The concentration of ferric ions was significantly higher in HRT users compared with that of controls in survey T2 and BGS98.

Other laboratory parameters in survey BGS98 only
Table 42 lists laboratory measurements from survey BGS98 only. Steroid hormone users both for contraception and for HRT had significant lower concentrations of glutamic pyruvic transaminase (GPT), lipoprotein A and antithrombin than controls. In addition, concentrations of fibrinogen, helicobacter pylori and fructosamine were also significantly lower in HRT users, which was not found in contraceptive users.

6. Multivariate unconditional logistic regression for the use of steroid hormones

All ORs and 95% CI of age groups were obtained from logistic models from general women populations (hormone users *vs.* nonusers, <50 years of age in Table 43 and ≥ 35 years of age in Table 44) after adjustment for other covariables in the table, whose ORs and 95% CIs were derived from logistic models from each studied population (users *vs.* controls) (Table 43 and Table 44).

Multivariate logistic regression analysis showed that selected sociodemographic factors and personal lifestyle were closely associated with the use of oral contraceptives or HRT. These factors may vary in different surveys along with time. From Table 43, women who used contraceptives were more from large cities in the earlier survey of T0 (OR for small city: 0.59, p=.018), were more from middle cities in survey T2 (OR for middle city: 1.66, p=.010) and were more from small cities in survey BGS98 (OR for small city: 1.59, p=.019), indicating OC use spreading from large cities to small cities. Over-weighted women used contraceptives less often as normal and under-weighted women. In earlier surveys, more female smokers

(OR=1.43 and 1.47 for surveys T0 and T1, respectively), but also less college-educated women used contraceptives, which was not found in later surveys (T2 and BGS98). Women with higher household income tended to use contraceptives more frequently, particularly in the last survey of BGS98 irrespective of being the main household earner or not. Compared with single women, married women used less contraceptives (most ORs <1 or close to 1), though it was not statistically significant. No apparent difference was found for social class, sports and alcohol consumption in the use of contraceptives.

In addition, more women with hypertension, hyperlipidemia and regular cycles had used contraceptives than women without such a condition. And less contraceptive users might suffer hyperuricemia (OR: 0.29-0.52 in the first four surveys) (Table 43). OC use was closely related to the occurrence of regular cycles, hypertension, hyperlipidemia in most surveys.

From Table 44, HRT users were more in large cities, especially in the earlier surveys (most ORs <1), had normal or lower body weight (all ORs >1 with statistical significance in surveys T1, T2 and BGS98), tended to be smoking-quitters, had more sports hours per week, and came from higher social class. HRT use might be associated with higher incidence of arthritis and gastritis and with lower incidence of diabetes.

PART 2: ANALYTICAL EPIDEMIOLOGICAL STUDIES

This part includes 4 independent case-control studies derived from the five National Health Surveys concerning the occurrence of hypertension and hyperlipidemia in association with contraceptive use in younger adult women (<45 years old) as well as the occurrence of diabetes and arthritis in association with HRT use in elderly women (≥45 years old).

Cases of hypertension, hyperlipidemia and diabetes were identified from each survey by measuring blood pressures, blood concentrations of lipids and fasting blood glucose, respectively, while considering those who were undergoing medications.

The definition of hypertension, hyperlipidemia and diabetes has been described above in the first part of 'Results' (see section 3.4.2). Cases of arthritis were reported by health survey participants with the verification of clinical physicians by medical interview. Controls of all above cases were randomly chosen in each single survey to yield an age distribution similar to that of cases (usually matched on age within 5 years), the method of which has also been described in 'Materials and methods'. Odds ratios and 95% confidence intervals obtained from logistic regression models were used to evaluate relative risks regarding to hormone use. Meanwhile, risks of the dose of estrogens contained in the contraceptives (low-dose and high-dose estrogens), the profile of contraceptives (monophasic and multiphasic contraceptives), regime of hormone replacement therapy (opposed and unopposed HRT) and estrogens used in either regime (conjugated and non-conjugated estrogens) were also evaluated.

1. Occurrence of hypertension in association with contraceptive use in young adult women (<45 years)

1.1 Descriptive characteristics for hypertensive patients and controls (Table 45)

The number of hypertensive patients and controls together with other selected descriptive characteristics are listed in Table 45. The average age of hypertensive patients was approx. 36 years. In all surveys, hypertensive patients had a significantly higher BMI and a significant higher prevalence of hyperlipidemia than their controls and no difference was found in the blood concentration of sodium. The use of contraceptives tended to be higher in hypertensive patients compared with their controls.

1.2 Risk of hypertension in association with contraceptive use (Table 46)

Survey T012 in Table 46 (and later in Table 48, 50 and 52) was the merging of surveys T0, T1 and T2 because of the relative homogeneity of these three surveys in social economic background, so that a relative large sample size could be obtained. From Table 46, contraceptive use was closely related to an increased risk of hypertension with ORs 1.59 (1.08-2.34), 1.57 (1.01-2.46), 1.37 (0.93-2.01) and 1.56 (1.09-2.24) in surveys T1, T2, T3 and BGS98, respectively. After adjustment for influence factors such as residence, BMI, education, smoking, social class, sports activities, alcohol use, etc., the ORs were enhanced to 1.90 (1.26-2.88), 1.75 (1.09-

2.80), 1.73 (1.14-2.63) and 1.68 (1.16-2.43), respectively, all of which were statistically significant.

Contraceptives containing low-dose estrogens (defined as less than 50 μg ethinyl estradiol or 75 μg of mestranol) showed a high OR with statistical significance in all surveys except for T0 after adjustment for influence factors. Though the ORs of contraceptives with high-dose estrogens (defined as 50 μg or more of ethinyl estradiol or 75 μg or more of mestranol) were 1.36 (0.91-2.04) and 1.50 (0.61-3.70) with no statistical significance for surveys T012 and BGS98, respectively, there were no differences to be found between OCs containing low-dose estrogens and OCs containing high-dose estrogens (Low vs high, adjusted OR 1.08 (0.68-1.72), 0.99 (0.54-1.83) and 1.10 (0.44-2.73) for survey T012, T3 and BGS98, respectively, data not shown in the table). Monophasic contraceptives were associated with an increased risk of hypertension in surveys T012, T3 and BGS98 whereas the OR of multiphasic contraceptives (bi- and triphasic contraceptives) was statistically significant only in survey T012 because of the contribution of survey T2, which showed an extremely higher OR 2.72 (1.53-4.84). OCs increase the risk of hypertension irrespective of estrogen dose (high and low) or profiles of OCs (monophasic and multiphasic OCs).

2. Occurrence of hyperlipidemia in association with contraceptive use in young adult women (<45 years)

2.1 Descriptive characteristics for hyperlipidemia patients and controls (Table 47)

According to the definition of hyperlipidemia described in section 3.4.2, more than 50% study subjects in all five surveys had suffered from hyperlipidemia, which made it impossible to find enough controls for hyperlipidemia cases especially in the elderly age groups. Therefore, hyperlipidemia was here redefined according to the guidelines of the American Heart Association and the NCEP Adult Treatment Panel III (NCEP ATP III) [103]: total cholesterol concentration >=6.2 mmol/L or triglycerides concentration >=2.3 mmol/L or those undergoing lipid-lowering therapy. Table 47 shows the number of hyperlipidemia patients according to the new definition together with other selected descriptive characters. Notably, hyperlipidemia patients had a significant higher BMI in all surveys and a higher incidence of hypertension in the first

three surveys compared with their controls. Cases from T2 were different from their controls in smoking, social class, education and contraceptive use.

2.2 Risk of hyperlipidemia associated with contraceptive use (Table 48)

No associations of hyperlipidemia with contraceptive use were found in surveys T3 and BGS98 irrespective of the adjustment of influence factors. It seems that contraceptive use was associated with increased risk of hyperlipidemia only in the earlier surveys with ORs 1.36 (1.11-1.68) before the adjustment and 1.43 (1.15-1.77) after the adjustment for survey T012. Overall, adjustment for influence factors did not change the values of ORs very significantly. The same was true for the risk of estrogen dose and the risk of contraceptives preparation. Both contraceptives containing low-dose estrogens and contraceptives containing high-dose estrogens increased the risk of hyperlipidemia with adjusted ORs 1.46 (1.14-1.89) and 1.37 (0.97-1.92), respectively. The ORs of monophasic contraceptives and multiphasic contraceptives were 1.48 (1.13-1.93) and 1.36 (1.00-1.86), respectively.

3. Occurrence of diabetes in association with HRT use in the elderly women (≥45 years)

3.1 Descriptive characteristics for diabetic patients and controls

According the fasting glucose concentration (≥7 mmol/L), 102, 142, 119, 72 and 196 diabetic patients were identified among women over 45 years old from the five surveys (Table 49). Compared with their controls, diabetes patients in each survey had a significantly higher BMI, came less from the upper social class and suffered more from hypertension. The use of HRT was very low both in diabetic patients and controls in surveys T0, T1 and T3 relative to that in surveys T2 and BGS98. In addition, diabetic patients from survey BGS98 significantly differed from their controls in smoking status, alcohol use.

3.2 Risk of diabetes in association with HRT use (Table50)

Because the total HRT use in surveys T0, T1 and T3 was very low, some ORs could not be calculated in T0 and T3, and the 95% CIs of ORs were wide in these surveys. Though not statistically significant, the results of T2 and T012 showed the same trends as BGS98: HRT use was associated with a decreased risk of diabetes defined on the fasting glucose concentration. In BGS98, use of HRT reduced the risk of

diabetes by two thirds (OR 0.32, 95% CI 0.13-0.78). Though both regimes (opposed and unopposed) showed the same trend of decreased risk of diabetes, opposed regime of estrogen plus progestogens appeared more efficacious in the reduction of diabetes risk. Contrary to the results of other four surveys, results of survey T3, though not statistically significant, shows an increased risk of diabetes for HRT use (Table 50).

4. Occurrence of arthritis in association with HRT use in the elderly women (≥45 years)

4.1 Descriptive characteristics for arthritis patients and controls

Arthritis is a chronic disease, occurring very often in the elderly. The number of arthritis patients is therefore relatively large (Table 51). Compared with their controls, arthritis patients showed significantly higher BMI in all surveys and alcohol consumption in the first two surveys; there was no significant difference for the other selected descriptive characteristics in Table 49 such as smoking status, social class, education.

4.2 Risks of arthritis in association with HRT use (Table 52)

After the adjustment for influence factors, surveys T2 and BGS98 showed the same trend of an increased risk of arthritis in HRT users with ORs 1.61 (1.10-2.36) and 1.33 (1.03-1.72), respectively. In the first three surveys, HRT products with non-conjugated estrogens were associated with an increased risk of arthritis (OR 1.57, 95% CI 1.09-2.25) whereas in BGS98, HRT products with conjugated estrogens were associated with an increased risks of arthritis (OR 1.75, 95% CI 1.10-2.78).