

Population-scale reconstruction of menopause dynamics reveals a physiological cliff at the final menstrual period

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Supplementary information for: Population-scale reconstruction of menopause features reveals a physiological cliff at the final menstrual period

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Table S1. Menopausal hormone therapy (MHT) usage in NHANES by variable, minimum 10 observation pairs. Population totals for menopausal females with all needed variables, includes: combo pill (or both estrogen and progestin): 127, estrogen pill: 512, progestin pill: 9, unknown: 4, not on mht: 7110. *Mann-Whitney U test (paired). We used paired tests for p values and effect sizes in this table (N pairs), whereas we used unpaired values for Fig 3 (N MHT and N control), hence Fig 3 effect sizes differ slightly.

Variable	System	N pairs	N MHT	N contro l	Contro l - MHT	Standar d error	p (U test*)	p (FDR adj.)	N Clalit
sodium	kidney	673	708	702	-0.371	0.061	3E-08	3E-07	3593
potassium	kidney	674	709	702	-0.153	0.065	0.02	0.04	-
bicarb	kidney	673	709	701	-0.171	0.052	8E-04	0.002	-
u creatinine	kidney	720	732	725	0.067	0.053	0.3	0.4	-
cystatin	kidney	304	378	384	-0.397	0.083	4E-06	3E-05	-
b2m	kidney	304	378	384	-0.353	0.095	5E-04	0.002	-
osmolality	kidney	676	710	703	-0.458	0.063	4E-12	1E-10	-
scr	kidney	671	708	700	-0.022	0.056	1	1	-
bun	kidney	676	710	703	-0.125	0.053	0.01	0.03	-
u albumin	kidney	719	731	725	-0.076	0.054	0.09	0.2	-
dhea	gonad	0	0	0	-	-	-	-	-
17-ohp	gonad	7	23	42	-	-	-	-	-
andro	gonad	7	23	42	-	-	-	-	-
calcium	bone	675	710	702	-0.228	0.056	6E-05	3E-04	3235
phosphate	bone	676	710	703	-0.275	0.052	2E-07	2E-06	2512
pth	bone	50	150	165	-0.369	0.199	0.03	0.06	-
alp	liver	419	533	547	-0.425	0.066	7E-10	1E-08	3635
bone alp	bone	37	134	129	-0.746	0.206	0.001	0.004	-
nfl	cognition	0	13	12	-	-	-	-	-
testo	gonad	33	87	121	-0.841	0.307	0.02	0.04	-
e2	gonad	31	67	116	0.628	0.209	0.003	0.009	-
fsh	gonad	56	159	174	-0.458	0.159	9E-04	0.003	-
lh	gonad	7	23	42	-	-	-	-	-
progsterone	gonad	7	23	42	-	-	-	-	-
shbg	liver	31	67	118	0.256	0.205	0.2	0.3	-
amh	gonad	7	23	42	-	-	-	-	-
e1	gonad	7	22	41	-	-	-	-	-

troponin	heart	306	380	383	-0.291	0.074	1E-04	6E-04	-
bnp	heart	303	377	383	0.090	0.095	0.1	0.2	-
ck	muscle	70	132	186	-0.160	0.169	0.4	0.5	-
apob	lipid metabolism	40	145	117	-0.065	0.156	0.7	0.8	-
homocysteine	kidney	140	270	285	-0.446	0.120	5E-04	0.002	-
sbp	heart	639	693	671	-0.004	0.074	1	1	-
map	heart	635	691	668	0.006	0.057	0.9	1	-
pp	heart	635	691	668	-0.001	0.075	0.8	0.9	-
fibrinogen	clotting	163	288	267	-0.323	0.104	0.005	0.01	-
crp	inflammation	448	581	521	0.318	0.052	8E-10	1E-08	-
hsrnp	inflammation	25	60	102	0.068	0.300	0.5	0.6	-
neutrophils	wbc	701	721	718	0.087	0.048	0.1	0.2	-
monocytes	wbc	702	721	719	0.046	0.052	0.4	0.6	-
lymphocytes	wbc	700	721	717	0.081	0.059	0.3	0.5	-
platelets	clotting	703	722	719	0.231	0.053	5E-05	3E-04	-
wbc	wbc	703	722	719	0.091	0.050	0.09	0.2	-
eosinophils	wbc	702	721	719	-0.014	0.049	0.6	0.7	-
alt	liver	675	709	703	-0.204	0.046	2E-06	2E-05	1414
ast	liver	669	707	699	-0.146	0.050	0.002	0.005	3749
ggt	liver	673	710	700	-0.204	0.059	9E-05	4E-04	1917
bilirubin	liver	419	533	547	-0.017	0.054	0.6	0.7	-
albumin	liver	676	710	703	-0.176	0.039	2E-05	1E-04	2690
transferrin sat.	iron	130	292	267	0.015	0.071	0.9	0.9	-
iron	iron	676	710	703	0.104	0.037	0.007	0.02	1241
ferritin	iron	245	393	374	-0.152	0.082	0.06	0.1	895
b12	micronutrients	417	514	517	-0.055	0.072	0.4	0.6	-
folate	micronutrients	48	113	157	0.040	0.225	0.9	1	-
folate (rbc)	micronutrients	51	114	161	0.015	0.217	0.8	0.9	-
hemoglobin	iron	705	722	721	0.019	0.040	0.7	0.8	-
hematocrit	rbc	567	655	618	-0.016	0.051	0.6	0.7	-
mcv	rbc	704	722	720	0.132	0.036	0.001	0.004	4360
rdw	rbc	703	722	719	-0.246	0.036	2E-12	1E-10	3612
ldh	muscle	418	532	547	-0.414	0.066	2E-08	2E-07	1965

rbc	rbc	705	722	721	-0.156	0.054	0.006	0.01	-
tibc	iron	269	409	379	0.431	0.065	1E-09	1E-08	-
f glucose	glucose metabolism	164	368	351	-0.172	0.115	0.03	0.05	-
hba1c	glucose metabolism	698	720	714	-0.231	0.047	5E-07	4E-06	-
total chol	lipid metabolism	680	712	705	-0.113	0.050	0.02	0.04	-
ldl	lipid metabolism	149	352	333	-0.275	0.116	0.02	0.04	-
hdl	lipid metabolism	310	417	438	0.220	0.073	0.001	0.004	-
tri	lipid metabolism	676	710	703	0.021	0.047	0.6	0.7	-
insulin	glucose metabolism	160	364	343	-0.253	0.102	0.03	0.06	-
c-peptide	glucose metabolism	82	201	197	-0.307	0.158	0.04	0.08	-
bmi	glucose metabolism	707	724	719	-0.180	0.044	4E-04	0.001	-
gtt	glucose metabolism	29	119	93	-0.517	0.244	0.1	0.2	-
tsh	thyroid	21	105	69	0.184	0.222	0.7	0.8	-
ft4	thyroid	21	105	69	0.152	0.264	0.6	0.7	-
tt4	thyroid	21	105	69	0.436	0.267	0.1	0.2	-
ft3	thyroid	21	105	69	0.283	0.307	0.4	0.6	-
tt3	thyroid	21	105	69	0.130	0.321	0.6	0.7	-
thyroglobulin	thyroid	21	105	69	-0.071	0.416	0.8	0.9	-
selenium	metal	48	119	149	-0.260	0.173	0.2	0.3	-
lead	metal	647	705	675	-0.420	0.048	7E-17	5E-15	-
cobalt	metal	27	63	107	0.034	0.187	0.9	1	-
oxychloro dane	pop	23	110	128	-0.130	0.195	0.4	0.6	-
pcb074	pop	29	127	119	-0.241	0.265	0.6	0.7	-
total bmd	bone mass	6	32	53	-	-	-	-	-
total bmc	bone mass	6	32	53	-	-	-	-	-
femor neck bmd	bone mass	111	235	191	0.301	0.151	0.04	0.08	-
l1_bmd	bone mass	108	227	190	0.604	0.150	4E-04	0.001	-
l2_bmd	bone mass	89	205	181	0.851	0.195	1E-04	5E-04	-
l3_bmd	bone mass	99	213	186	0.702	0.176	2E-04	7E-04	-

I4_bmd	bone mass	93	204	181	0.972	0.209	3E-05	2E-04	-
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Table S2. Clinical outcome variables in NHANES (females)

Variable	System	N obs	NHANES Code	Description	Notes
anemia	rbc	36308	MCQ053	Taking treatment for anemia/past 3 mos	
angina	heart outcome	36234	MCQ160D	Ever told you had angina/angina pectoris	
arthritis	bone outcome	36267	MCQ160A	Doctor ever said you had arthritis	
asthma	lung	36328	MCQ010	Ever been told you have asthma	
bronchitis	lung	27322	MCQ160K	Ever told you had chronic bronchitis	
copd	lung	8691	MCQ160O	Ever told you had COPD?	
depress score	depression	23721	DPQ0(1-9)0	Sum, NAs imputed with average	
diabetes	misc outcome	36328	DIQ010	Doctor told you have diabetes	borderline or worse
diff falling asleep	sleep	2486	SLQ080	How often have trouble falling asleep?	
emphysema	lung	27345	MCQ160G	Ever told you had emphysema	
ever smoke	smoking	36306	SMQ020	Smoked at least 100 cigarettes in life	
gout	kidney outcome	17604	MCQ160N	Doctor ever told you that you had gout?	
heart attack	heart outcome	36291	MCQ160E	Ever told you had heart attack	

heart disease	heart outcome	36212	MCQ160C	Ever told you had coronary heart disease	
heart failure	heart outcome	36266	MCQ160B	Ever told had congestive heart failure	
insufficient sleep	sleep	2158	SLQ130	How often did you not get enough sleep?	
kidney disease	kidney outcome	36285	KIQ02(0 and 2)	Ever told you had weak/failing kidneys	
kidney stones	kidney outcome	22257	KIQ026	Ever had kidney stones?	
liver disease	misc outcome	36286	MCQ160L	Ever told you had any liver condition	
osteoporosis	bone outcome	21878	OSQ060	Ever told had osteoporosis/brittle bones	
sleep breathing	sleep	4861	SLQ120	How often feel overly sleepy during day?	
sleep disorder	sleep	14154	SLQ060	Ever told by doctor have sleep disorder?	
sleeping pills	sleep	4510	SLQ140	How often take pills to help you sleep?	
smoke now	smoking	36304	SMQ040	Do you now smoke cigarettes	
snore	sleep	8123	SLQ030	How often do you snore?	
stroke	heart outcome	36303	MCQ160F	Ever told you had a stroke	
thyroid problem	misc outcome	31243	MCQ160M	Ever told you had thyroid problem	
trouble sleeping	sleep	24586	SLQ050	Ever told doctor had trouble sleeping?	

wake up at night	sleep	2279	SLQ090	How often wake up during night?	
wake up early	sleep	2211	SLQ110	How often feel unrested during the day?	
weak grip	functional	4973	MGXH(1-2)T(1-3)	Male cutoff: 29 kg Female cutoff: 18 kg ¹	Max of 6 measurements = 3 trials x 2 hands

Table S3. Menopausal hormone therapy (MHT) drug classes in NHANES

We included prescription drug usage when considering MHT status. All drug classes labelled as e2 or combo were included as MHT (bolded). Note that we also included females who self-reported MHT usage without specifying the drug class.

NHANES code (RXDDRGID)	Drug class (RXDDRUG)	Label
a10899	ESTRADIOL; ESTRIOL; ESTRONE	e2
a10900	ESTRADIOL; ESTRIOL	e2
a11518	CONJUGATED ESTROGENS; PROGESTERONE	combo
a70248	ESTRIOL	e2
c00101	SEX HORMONES - UNSPECIFIED	excluded
c00102	CONTRACEPTIVES - UNSPECIFIED	contraceptive
c00183	ESTROGENS - UNSPECIFIED	e2
c00186	SEX HORMONES COMBINATION - UNSPECIFIED	unknown (excluded)
d00229	ETHINYL ESTRADIOL	e2
d00534	ESTRONE	e2
d00537	ESTRADIOL	e2
d00541	CONJUGATED ESTROGENS	e2

d00542	ESTERIFIED ESTROGENS	e2
d00543	ESTROPIPATE	e2
d00550	PROGESTERONE	progestin
d00554	HYDROXYPROGESTERONE	progestin
d00555	NORETHINDRONE	contraceptive
d00557	LEVONORGESTREL	contraceptive
d03034	NORGESTREL	progestin
d03238	ETHINYL ESTRADIOL; NORETHINDRONE	combo
d03240	MESTRANOL; NORETHINDRONE	combo
d03241	ETHINYL ESTRADIOL; NORGESTREL	combo
d03242	ETHINYL ESTRADIOL; LEVONORGESTREL	combo
d03245	ESTERIFIED ESTROGENS; METHYLTESTOSTERONE	e2
d03388	ETHINYL ESTRADIOL; ETHYNODIOL	combo
d03389	ESTRADIOL; TESTOSTERONE	e2
d03781	ETHINYL ESTRADIOL; NORGESTIMATE	combo
d03782	DESOGESTREL; ETHINYL ESTRADIOL	combo
d03819	CONJUGATED ESTROGENS; MEDROXYPROGESTERONE	combo
d04210	ESTRADIOL TOPICAL	e2
d04213	PROGESTERONE TOPICAL	progestin
d04375	ESTRADIOL; NORETHINDRONE	combo
d04396	CONJUGATED ESTROGENS TOPICAL	e2
d04506	ESTRADIOL; NORGESTIMATE	combo

d04721	ESTRADIOL; MEDROXYPROGESTERONE	combo
d04760	DROSPIRENONE; ETHINYL ESTRADIOL	combo
d04772	ETONOGESTREL	progestin
d04773	ETHINYL ESTRADIOL; ETONOGESTREL	combo
d04779	ETHINYL ESTRADIOL; NORELGESTROMIN	combo
d04914	ESTRADIOL; LEVONORGESTREL	combo
d05027	ESTRIOL	e2
d05530	DROSPIRENONE; ESTRADIOL	combo
d06272	DIENOGEST; ESTRADIOL	combo
d07697	DROSPIRENONE; ETHINYL ESTRADIOL; LEVOMEFOLATE	combo

References

1. Huemer, M.-T. *et al.* Grip strength values and cut-off points based on over 200,000 adults of the German National Cohort - a comparison to the EWGSOP2 cut-off points. *Age Ageing* **52**, (2023).