

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

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Menopause reshapes female physiology, yet current understanding is limited by small longitudinal cohorts that characterize it as a gradual transition. Large-scale biomedical datasets remain underutilized because the final menstrual period (FMP) age is rarely recorded. Here we present a computational framework, inspired by astronomy, that reconstructs FMP-anchored trajectories from cross-sectional data by removing the blurring caused by variation in FMP age across individuals. Applying this to two independent cohorts totaling 300 million laboratory tests revealed a step-like physiological cliff at the FMP including endocrine, skeletal, hepatic, renal and lipid systems. These discontinuities are absent in male individuals, are concordant across populations and appear markedly attenuated by menopausal hormone therapy. Dysregulation began more than a decade before FMP. These findings support a systemic, quantifiable view of menopause and provide a generalizable strategy for recovering hidden biological trajectories applicable to other transitions such as puberty or disease progression.

Menopause—the permanent cessation of menstruation—is an understudied transition in human health^{1–5}. Understanding the dynamics of menopause, how physiological systems respond to these dynamics and how early dysregulation begins is therefore central to understanding human physiology and health.

Menopause is due to exhaustion of ovarian follicles, with sizable sex hormone fluctuations in the years before menopause, ultimately leading to a drop in estrogen and progesterone and rise in FSH, with variability between individuals⁴. Because sex hormone receptors are expressed in almost all human tissues, with effects on brain, vasculature, bone, liver and adipose tissue^{6–8}, these hormonal dynamics reverberate beyond fertility to many physiological systems³.

The menopause transition was illuminated by prospective cohorts such as the Study of Women's Health Across the Nation (SWAN)^{5,9–12},

showing that sex hormone changes begin about 7 years before menopause⁵ and that bone loss accelerates in relation to menopause¹¹. Such longitudinal studies are crucial owing to their exquisite menopause documentation. However, longitudinal studies such as SWAN are limited in their number of participants, include only a small panel of laboratory tests and follow subjects for only a few years before the final menstrual period (FMP). Larger omics screens¹³ imply that menopause is a systemic inflection point, but the de facto use of age instead of menopause timing blurs the timeline of this onset, as sampling is done at an arbitrary time point for each participant relative to her FMP. Thus the field lacks both sample size and temporal resolution.

To address this, we develop a method to obtain detailed cross-sectional menopause dynamics from large medical datasets and apply this to more than 300 million laboratory tests from more than

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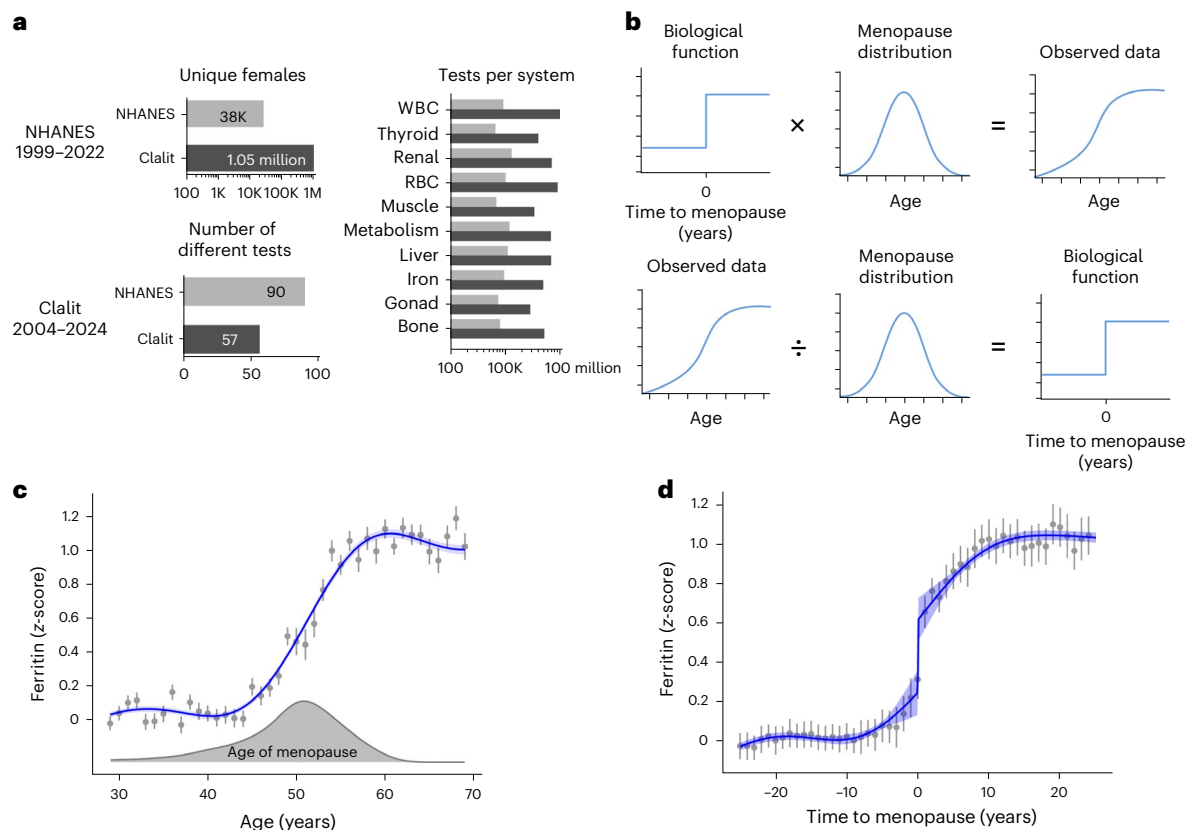


Fig. 1 | Physiological tests as a function of time from menopause show a jump. a, b, Overview of datasets (57/90 tests were in both studies) (**a**) and deconvolution approach (**b**). **c,** The representative trajectory of ferritin in female individuals as a function of age and the distribution of menopause ages (gray) from NHANES (smoothed with 1.5 year bandwidth). Blue line is a 10-knot spline. **d,** Ferritin, adjusted for time to menopause using the deconvolution approach,

shows a jump at menopause $t = 0$ (z-score compared with nonpregnant reference group; from NHANES). The blue line is an average of flexible models weighted by cross-validation (Methods). Error bars are standard errors of the mean. Ferritin $n = 19,452$ people, menopause events $n = 11,412$ people. K, thousand; WBC, white blood cell; RBC, red blood cell.

1 million female individuals. We build on a concept from astronomy that allows us to ‘deblur’ the trajectories by deconvolving the known menopause age-of-onset distribution—similar to the way an astronomical image is sharpened by adjusting for the distortion caused by the telescope¹⁴. We resolve fine temporal dynamics as a function of time to menopause, revealing physiology-wide jumps at the FMP, which appear to be normalized by hormone replacement therapy and are preceded by hormonal changes more than a decade before menopause.

Results

Analysis of two large datasets shows a jump at menopause in almost all physiological systems that is absent in male individuals

We analyzed two large datasets (Fig. 1a). The first is National Health and Nutrition Examination Survey (NHANES), a cross-sectional US health and aging study (1999–2022), with laboratory tests, health questions, exams and outcomes. The second is from health insurer Clalit, which includes about half the Israeli population, including 1.3 million female individuals aged 30–70 years in the years 2004–2024. Laboratory tests in this anonymized all-comers dataset were analyzed cross-sectionally. For each laboratory test, we omitted data from individuals who took medications or had ICD-9 codes that statistically affect that test^{15,16}. In both datasets, we considered only nonpregnant individuals (demographics in Table 1).

We sought to study laboratory tests as a function of time from menopause. Standard cross-sectional analysis shows that the population means of test values change gradually with age and, in female

individuals, shows a higher slope at ages 40–60. As an example, the iron-related test ferritin is shown in Fig. 1c.

The change around menopause is broadened owing to the different menopause time of each individual, defined by FMP. To distill the effect of time from FMP, we assumed that each test value is an unknown function of time to menopause $f(t)$ where $t \equiv a - a_m$ is the difference between an individual’s age a and their age of FMP a_m . We developed an approach to determine $f(t)$, including a possible step-like change at menopause, by deconvolving the known FMP time distribution¹⁷ from each laboratory test’s cross-sectional trajectory. The FMP age distribution in NHANES has a median of 50 years and interquartile range (IQR) of 45–53 years (Fig. 1c). We validated this method using simulated data and different forms of FMP distribution functions, including variations in average FMP age of 4 years, the observed range across human populations or major risk groups¹⁸ (Extended Data Figs. 1 and 2).

To clarify, our algorithm does not predict the FMP time for each individual. Instead, we deduce the cross-sectional mean trajectory of each laboratory test as if we knew the age of FMP for each individual and aligned the tests by time from FMP.

We find that both datasets show jumps at menopause in most of the laboratory tests. For example, the ferritin test adjusted for time to menopause shows a jump (step-like change) of 0.6 s.d., where s.d. is the standard deviation of log-scaled test value (z-score) compared with a control population of 25–45-year-old nonpregnant female individuals (Fig. 1c).

We show the dynamics in terms of time to menopause for 90 tests in Fig. 2 (Extended Data Tables 1 and 2). The YoGlen algorithm reveals

Table 1 | Demographic summary

	Median (IQR) or prevalence (s.e.m.)	Number of observations	Missing	Median (IQR) or prevalence (s.e.m.)	Number of observations	Missing
NHANES	Female			Male		
Age (years)	51 (36–66)	36,287	0.0%	51 (35–66)	34,440	0.0%
BMI (kg m ⁻²)	28 (24–34)	32,896	9.3%	28 (24–33)	31,398	8.8%
Smoke	16% (0%)	36,235	0.1%	24% (0%)	34,386	0.2%
Post menopause	48% (0%)	26,567	14.0%	–	–	–
Menopause age	50 (45–53)	11,412	20.0% ^a	–	–	–
Current MHT use ^b	9% (0%)	11,443	38.6%	–	–	–
Current birth control use ^c	12% (0%)	7,684	43.8%	–	–	–
Clalit	Female			Male		
Age (years)	49 (35–62)	1.32million	0.0%	55 (41–65)	1.2million	0.0%
BMI (kg m ⁻²)	28 (24–33)	923,000	30%	28 (25–31)	886,000	26%

^aSelf-reported postmenopausal female individuals only (premenopausal women were treated as censored at their current age). ^bSelf-reported menopausal female individuals only; varies greatly by study year (Extended Data Fig. 8). ^cSelf-reported nonmenopausal female individuals only; self-reported birth control use (‘yes’ ever used, RHQ420, and ‘yes’ currently use, RHD440/RHD442) or reported use of estrogen–progestin contraceptive.

jumps at menopause in female individuals (Extended Data Fig. 3), but not in male individuals (Extended Data Fig. 4). Female individuals showed a significant jump in 52/90 laboratory tests (z-test versus male individuals, false discovery rate (FDR) corrected). Jump sizes ranged from 0.1 to 1.4 s.d.

We compared these with male individuals, where we perform the same adjustment as female individuals by deconvolving the same FMP distribution (apparent menopause time $t = 0$ for male individuals can be interpreted as age 50). Male individuals did not show jumps around $t = 0$, and instead, their mean laboratory tests changed gradually (Fig. 2a, blue lines).

In female individuals, large jumps (≥ 0.5 s.d.) are found in sex hormones, including estradiol (E2), anti-mullerian hormone (AMH) and follicle-stimulating hormone (FSH). These jumps are consistent with longitudinal data on E2 and FSH from SWAN (Extended Data Fig. 5). More surprising is the prevalence of such jumps in almost all other physiological systems—liver tests, blood counts, blood chemistry, kidney functions, bone tests, lipids and osmolality (Fig. 2b).

Despite differences in population, context and study design, the Clalit and NHANES datasets show strongly correlated jump sizes ($r = 0.89$, $P = 10^{-16}$). We also tested the sensitivity to age range and use of only participants with recorded menopause status and found excellent agreement ($r > 0.95$, $P = 10^{-16}$; Extended Data Fig. 6).

Most of the observed jumps are for the worse in the sense that they are in the direction of increased disease risk. The main exceptions are tests related to iron, hemoglobin and red blood cells. The latter tests improve (move in the direction of less anemia) probably owing to the cessation of menstrual bleeding¹⁹.

Menopausal hormone therapy appears to reduce the physiological jumps at menopause

We tested the effect of menopausal hormone therapy (MHT, previously called hormone replacement therapy) on the dynamics of laboratory tests. We used NHANES female individuals with self-reported post-menopause status taking estrogen-containing drugs and/or those that answered the NHANES question taking (estrogen, progestin or combination) pill now. As this group amounted to only 9% of the participants, it may differ from the rest of the cohort in symptoms, access to healthcare and other factors. We therefore used two methods to adjust for economic and lifestyle characteristics: propensity score matching²⁰ and linear regression (Methods). Both methods produced concordant results ($r = 0.90$, $P = 10^{-16}$; Extended Data Fig. 7). We specifically adjusted

before versus after 2004, the year in which MHT usage dropped dramatically (Extended Data Fig. 8).

Overall, 39/80 of the tests were different between MHT and non-MHT cohorts (Mann–Whitney U test, FDR-corrected, minimum 10 propensity score-matched individuals per test). This includes bone-dependent tests (bone mineral density (BMD), bone ALP and calcium), osmolality and sodium, liver tests (albumin, ALP, ALT, bilirubin and GGT) and renal tests (cystatin C and homocysteine). Several additional tests show a trend for an effect that did not reach significance (9/80, $P < 0.1$, U test; Supplementary Table 1).

We find that the size of most of the jumps at menopause is reduced in participants that reported current MHT usage (Fig. 3a). The bigger the test jump at menopause, the larger the correction seen in MHT, Pearson’s $r = 0.76$ (95% confidence interval (CI) 0.65–0.84, $P = 10^{-15}$; without iron and red blood cell (RBC) $r = 0.81$, 95% CI 0.64–0.85, $P = 10^{-13}$). We also analyzed tests by system to find that in most systems that showed a significant jump, notably excepting C-reactive protein (CRP) and iron/RBC, the absolute jump magnitude was significantly lower in the MHT cohort (Fig. 3b) especially in the bone, liver and kidney/osmolality systems.

We compared the NHANES findings with Clalit. We analyzed female individuals from Clalit who were prescribed MHT drugs (Angeliq or Eviana) at least twice ($n = 9,103$). We used a longitudinal design, comparing these female individuals before, during and after MHT use. We compared with control female individuals from the same clinic, age and birth year. We find moderately strong concordance between the MHT effect sizes with NHANES ($r = 0.63$, $P = 0.005$) (Methods).

We conclude that MHT appears to reduce the jump-like change at menopause, making the postmenopause traces resemble a smoother continuation of the premenopausal traces.

Sex hormone dysregulation begins more than a decade before the FMP

Three major sex hormones showed a marked change in dynamics long before the FMP (Fig. 4). AMH begins an accelerated drop at about 15 years before menopause in its mean cross-sectional trajectory (Fig. 4a,d). The gonadotropin FSH begins an accelerated rise about 14 ± 1 years before menopause. E2 begins an accelerated drop about 12 ± 1 years before menopause. Change point analysis of Clalit deconvolved trajectories shows nearly identical times for the dysregulation of E2 and FSH (Fig. 4, purple lines; Clalit AMH had insufficient data). These E2 and FSH changes are about 7 years earlier than documented in previous studies⁵ (Fig. 4).

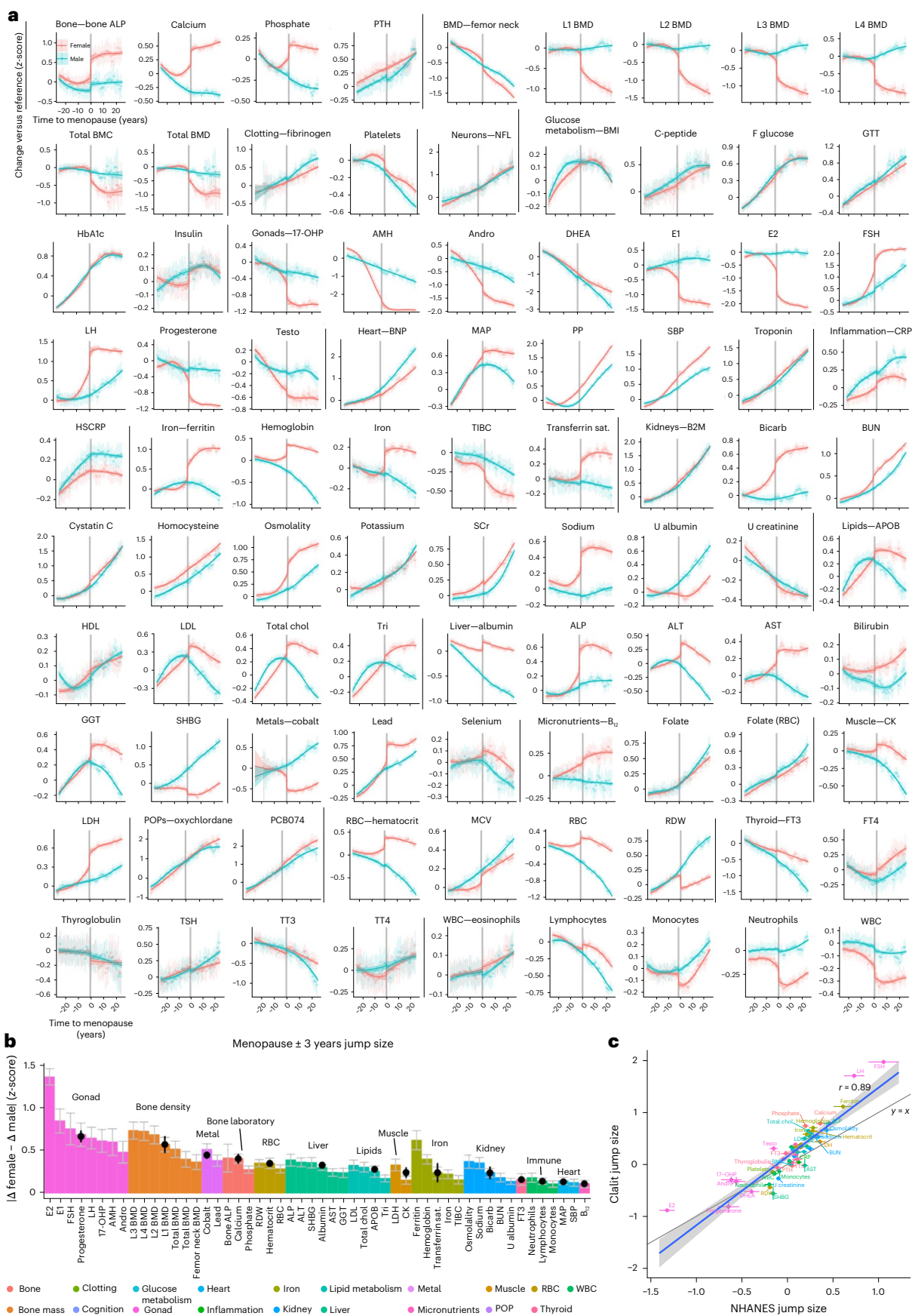


Fig. 2 | Tests show jumps across systems in female individuals but not male individuals, and jump sizes are similar in the two datasets. **a**, 90 laboratory tests from NHANES as a function of time to menopause, grouped by system. Female individuals (red) often show a jump at $t = 0$, whereas male individuals (blue) do not (male data was deconvolved in the same way as female individuals). Error bars are standard error of the mean. Lines are flexible model averages weighted by cross-validation (Methods). **b**, NHANES jump sizes ordered by system; black points are median for each system (3-year change for female

individuals minus male individuals; all $P < 0.05$, two-sided z-test, FDR corrected). **c**, Jump size in NHANES and Clalit datasets show high correlation ($r = 0.89$, $P = 10^{-16}$, Pearson's two-sided test). Jump sizes in **b** and **c** are mean and standard error from cross-validated model estimates (from 'The YoGlen algorithm' section in the Methods). NHANES median $n = 14,778$, IQR 5,481–29,431 people (Extended Data Table 1); Clalit median $n = 3$ million, IQR 1–7 million tests (Extended Data Table 2). POP, persistent organic pollutant. Abbreviations are defined in Extended Data Table 1.

The variation (s.d.) of hormone levels rises in the decade before the FMP (Fig. 4g–i). This is consistent with sex hormone fluctuations²¹ and cycle irregularity²² in the late menopause transition.

Mean E2 increases from 25 to -12.5 years before menopause (Fig. 4c), and its variation decreases (Fig. 4i). This is consistent with reports that cycles become more regular and the follicular phase shortens from ages 25–40 (-25 to 10 years before menopause)²².

Prevalence of health deficits show increased slope after menopause

As most physiological laboratory tests show a jump-like shift at menopause, we used our deconvolution approach to ask about clinical outcomes as a function of time to menopause using data from NHANES. These health deficits include diagnoses of diabetes, osteoporosis, liver disease, heart disease and symptoms such as trouble falling asleep.

Most of the deficits rise in prevalence after menopause. Several deficits also show a small jump at the FMP (Fig. 5). Osteoporosis has a rise in slope at the FMP (Fig. 5a), strongly outpacing male individuals, consistent with the large effects of the menopause transition on bone tests. Cardiovascular outcomes (heart attack and stroke) also accelerate after menopause (Fig. 5b).

Anemia was the only major clinical outcome that showed a drop in prevalence at menopause (Fig. 5c)—consistent with the stop of menstruation leading to improved iron and RBC laboratory tests (difference in log-odds ratio versus male individuals at FMP ± 3 years, -0.63 ± 0.14 , $P < 10^{-3}$, FDR adjusted).

Thyroid and kidney outcomes are weakly affected by menopause, consistent with the relatively minor effect of menopause on renal function tests (creatinine and cystatin) and thyroid tests (Fig. 2).

Whereas the prevalence of most clinical outcomes rises after menopause and stays high, depression scale ratings (PHQ-9) showed a transient rise on average (Fig. 5d). Moderate and severe depression rates (PHQ-9 above 10) in postmenopausal female individuals with self-reported menopause timing were significantly elevated in the year after menopause (46/236 = 19%) compared with the subsequent 24 years (698/6,495 = 11%; Fisher test, $P < 10^{-4}$). Several symptoms and behaviors also rise transiently after menopause and then decay to the slower aging-like behavior seen in male individuals. This includes difficulty falling asleep and insufficient sleep (Fig. 5e).

Male individuals also show a change in slope of prevalence curves around age 50 with no detectable jump. The gap between male individuals and female individuals widens for several clinical outcomes, with bone-related outcomes and thyroid showing increasingly higher prevalence in female individuals. The gap between male individuals

and female individuals narrows for anemia, liver disease and several sleep deficits after menopause.

Discussion

We analyzed two large datasets totalling more than 300 million laboratory tests, indicating that menopause is characterized by a 'physiological cliff', defined as abrupt, step-like changes across nearly all physiological systems. We introduce a temporal deconvolution framework that uses cross-sectional data to generate a high-resolution timeline anchored to the FMP. This can detect systemic shifts that are typically obscured by chronological age. The observed jumps at the FMP are concordant between the USA (NHANES) and Israel (Clalit) cohorts. The changes are most pronounced in systems such as bone metabolism, liver tests, lipid handling and osmolality. While prior longitudinal studies, such as SWAN, have established bone loss and specific hormonal surges, the scale of this study, covering 90 types of tests, demonstrates that this transition is sharp and systemic.

The magnitude of the jump in each test corresponds in part to the differential sensitivities of physiological systems to estrogen (Fig. 2b). The large change of upstream hormones such as FSH is due to their exquisite estrogen sensitivity via negative feedback in the hypothalamic–pituitary–ovarian axis. Bone is very sensitive to the protective effects of estrogen²³, followed by the liver⁸, which is a hub for lipid metabolism. Osmolality is regulated by antidiuretic (ADH) hormone (also called arginine vasopressin), whose sensitivity is governed by estrogen²⁴. Toxin levels such as lead also show a jump in menopause, probably due to the bone storage of lead²⁵.

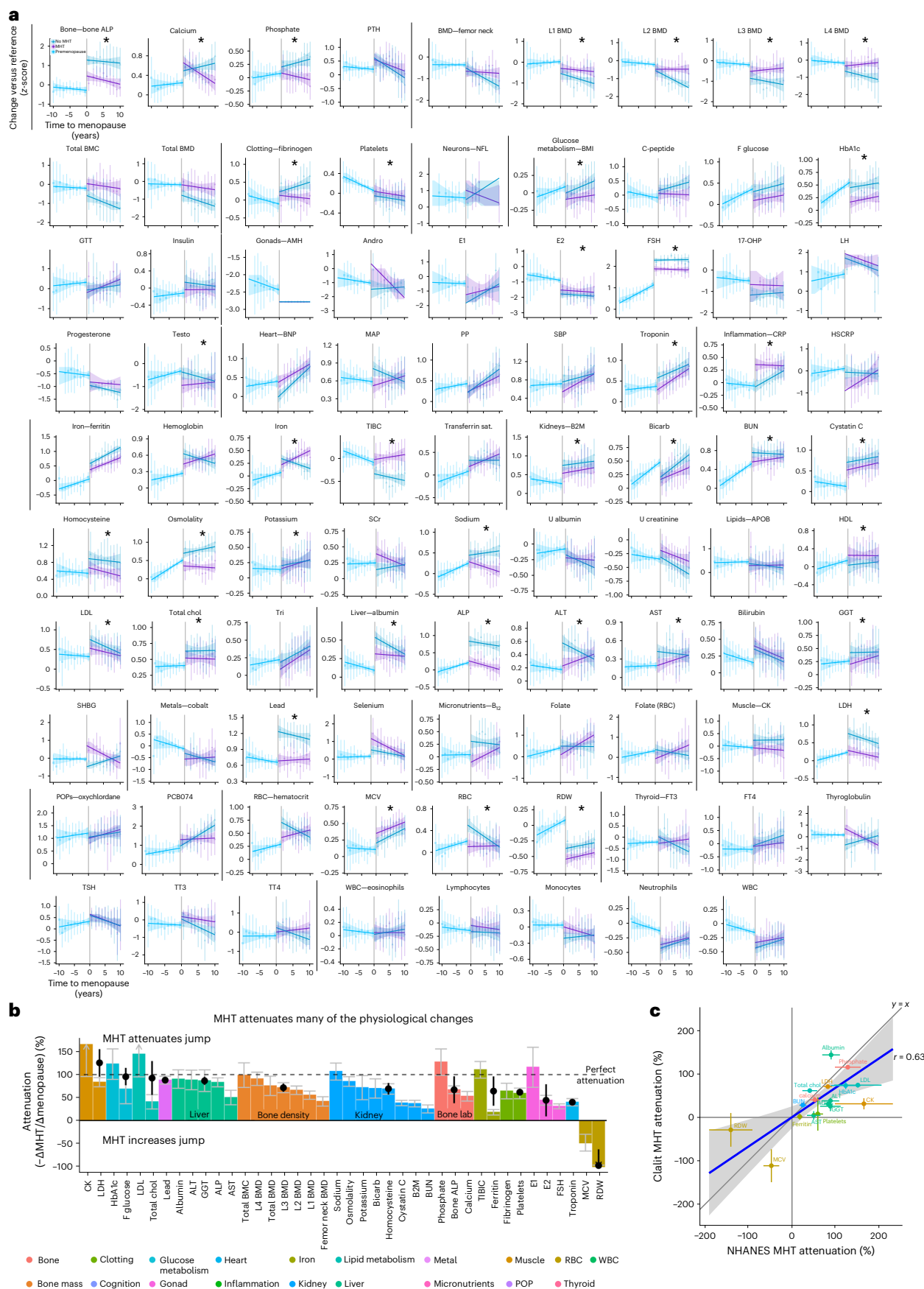
Several tests showed no detectable jumps at the FMP, including free thyroid hormones²⁶, PTH²⁷, folate²⁸ and fibrinogen²⁹. These systems are known to be weakly, indirectly or debatably affected by estrogen and menopause. The jumps are preceded by accelerated changes in sex hormones more than a decade before menopause, earlier than the 3–7-year window traditionally ascribed²¹.

Notably, we find that male individuals lack these abrupt physiological shifts, suggesting that the cliff is a consequence of the menopausal transition rather than general aging.

These laboratory test shifts are associated with a rise in risk for various clinical outcomes, which manifest in our analysis as an increase in the slope of incidence at the FMP. Thus, prevalence is akin to an integral over time of the laboratory test trajectory. For instance, osteoporosis shows an increase in slope after menopause that strongly outpaces that of age-matched male individuals, consistent with the large effects observed in bone-related laboratory tests. Cardiovascular outcomes, such as heart attack and stroke, also demonstrate an increased risk

Fig. 3 | Menopause hormone therapy appears to reduce jumps in many systems. **a**, NHANES laboratory tests as a function of time to menopause comparing participants with current MHT use (purple) to propensity score-matched controls (blue; median $n = 378$, IQR 114–710 with test and taking MHT; Supplementary Table 1); matched premenopause participants also in blue. Lines are linear fits, points are imputed mean, and bands are standard error. Star marks significant MHT effects (FDR-corrected paired two-sided Mann–Whitney U test $P < 0.05$). **b**, Jump attenuation defined as the ratio of mean jumps in MHT versus control, (MHT-pre)/(control-pre), shown are significantly changed tests (FDR-corrected unpaired two-sided z-test $P < 0.05$); 100% attenuation indicates complete abolition of the jump at the FMP, and negative values mean a larger

jump in the MHT cohort. Tests are grouped by system, black points are the median $\pm$ mean absolute deviation of the system. All laboratory tests have at least ten measurements for each group (MHT now, no MHT and premenopause). Values are unpaired median ($\pm$ mean absolute deviation) attenuation from 1,000-repeat bootstrapping. **c**, NHANES and Clalit show moderate–strong agreement on MHT attenuation for the overlapping variables from **b** ($r = 0.63$, $P = 0.005$, Pearson's two-sided correlation; including only Clalit variables with >200 individuals; Methods). Points are mean with standard error. NHANES median $n = 378$, IQR 114–710 people with each test and taking MHT; Clalit median $n = 2,690$, IQR 1,917–3,612 tests; Supplementary Table 1. Abbreviations are defined in Extended Data Table 1.



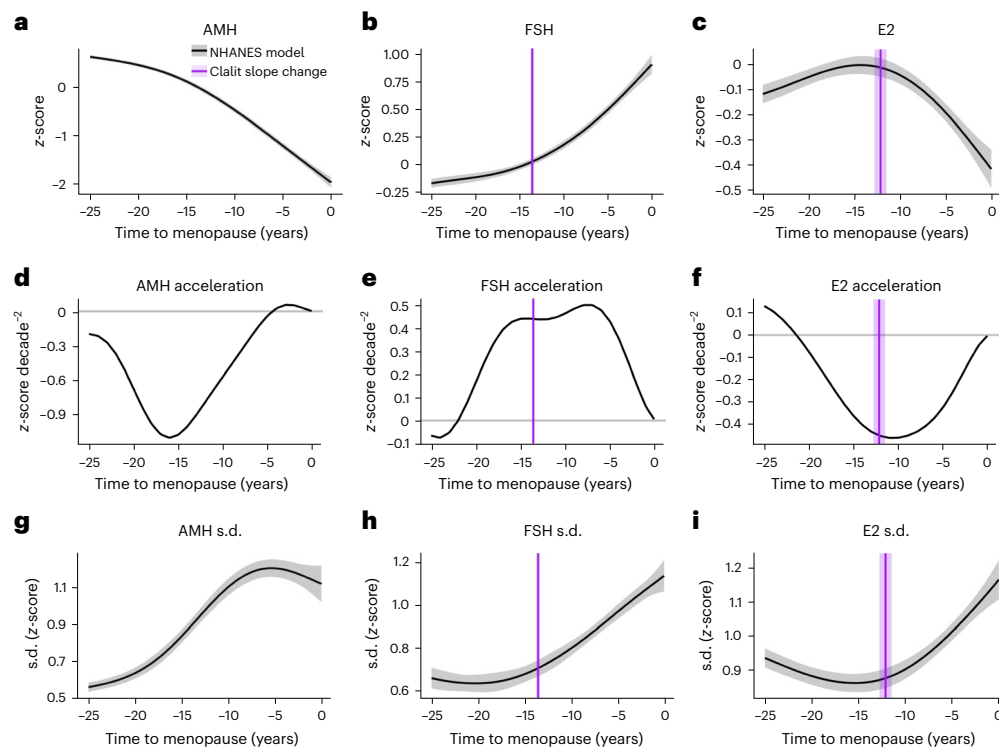


Fig. 4 | Sex hormones show accelerated change more than a decade before menopause. **a–c**, Cross-sectional means in the 25 years before the FMP from NHANES female individuals who are self-reported nonmenopausal for AMH (**a**), FSH (**b**) and E2 (**c**) ($n = 2,406, 3,035$ and $4,621$, for AMH, FSH and E2, respectively). Purple lines are slope change points from the Clalit dataset (Methods). **d–f**, The acceleration (second derivative by time, also called curvature) of

hormone traces: AMH (**d**), FSH (**e**) and E2 (**f**); change points are located at the start of large accelerations (positive or negative). **g–i**, The s.d. of hormones: AMH (**g**), FSH (**h**) and E2 (**i**). All measures are based on z-scores of log test values. Lines are Gaussian location-scale model prediction with standard error from ten-repeat, tenfold cross-validation. Acceleration is the discrete derivative using a local polynomial after 0.1-year bandwidth smoothing (no errors).

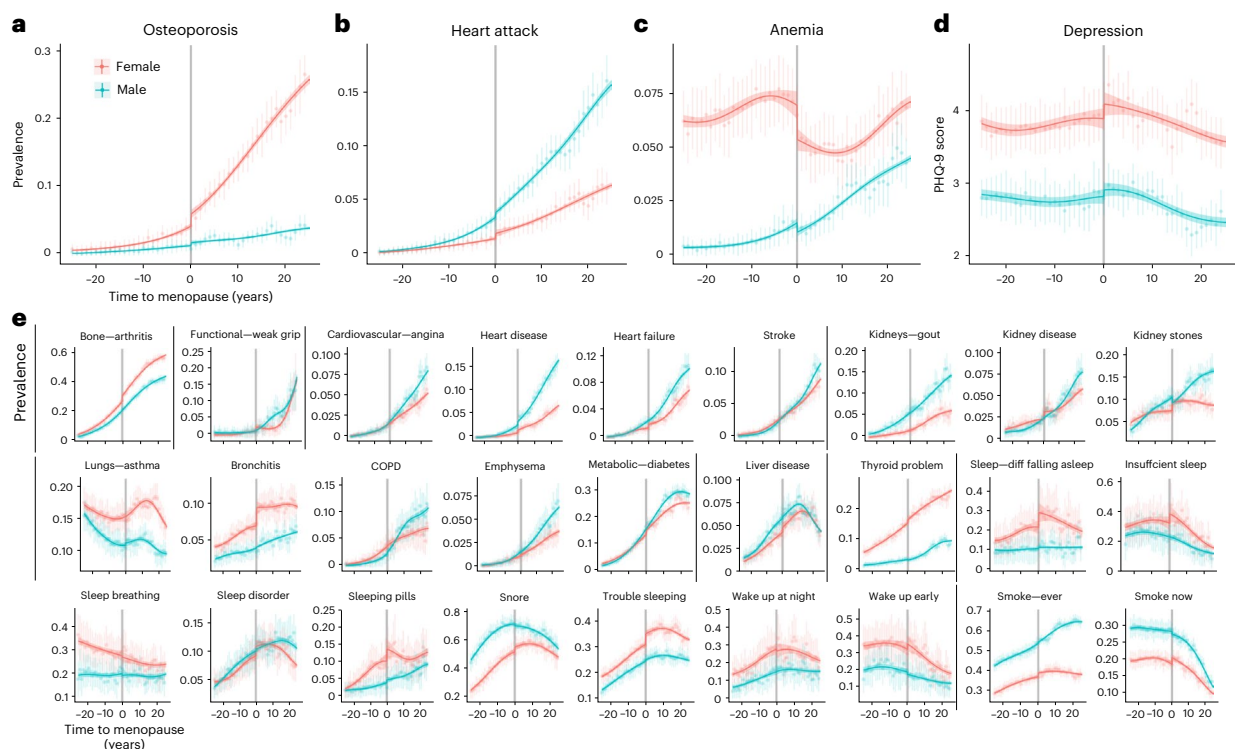


Fig. 5 | Health outcomes and deficits generally show increased slope after menopause. **a–e**, Prevalence in NHANES of osteoporosis (**a**), heart attack (**b**), anemia (**c**), depression score (**d**) and 27 additional outcomes and deficits organized by system (**e**). Female individuals (red) and male individuals (blue).

Lines are flexible model averages, weighted by cross-validation (Methods). Points are mean with standard error. Median $n = 27,322$, IQR $8,407–36,285$ people (Supplementary Table 2). PHQ-9, patient health questionnaire-9; COPD, chronic obstructive pulmonary disease.

slope following the transition. Furthermore, we observed a transient rise in average depression scale ratings and sleep-related deficits around the time of the FMP, which then tend to decay back toward the slower aging patterns seen in male individuals. We note that although the average rise in depression scores is transient¹², a subset of female individuals are known to show sustained depression post menopause³⁰.

Collectively, these findings suggest that the abrupt shifts in laboratory markers serve as a systemic inflection point for the accumulation of clinical health deficits.

Menopause hormone therapy appeared to markedly attenuate the physiological shifts. In female individuals reporting current MHT use, postmenopausal trajectories resembled smoother continuations of premenopausal states across various markers, including liver, renal and bone tests. While MHT appeared to normalize most systems, it was associated with elevated CRP, an inflammation marker. This is consistent with studies that show that MHT estrogen stimulates hepatic CRP production in oral but not transdermal (patch) treatment owing to a first-pass hepatic effect^{31,32}. In general, MHT is anti-inflammatory^{33,34}.

This study has several important limitations. It relies on retrospective cross-sectional data and self-reported menopause status. While deconvolution sharpens the timeline, it cannot replace the granularity of a prospective longitudinal study with detailed menopausal tracking that follows the same individuals through the transition. Adjusting for sociodemographics cannot entirely eliminate healthy user bias among MHT users, because those who choose or have access to MHT may differ intrinsically from nonusers in ways not captured by medical records or demographic data. The effects of MHT need to be tested by prospective randomized trials. The accuracy of our timelines also depends on the assumed distribution of FMP age, and while sensitivity analyses showed negligible effects to shifting this distribution, more accurate menopause tracking is warranted. Finally, while we controlled for many drugs, the lack of comprehensive data on hormonal IUDs or endometrial ablations in some cohorts could mask the true FMP for a subset of participants.

Our deconvolution approach is based on a latent variable formalism that is applicable to other biological transitions with unknown timing (Methods).

These findings further support a systemic and quantifiable view of the menopausal transition. We observed a physiological cliff at menopause across systems, which appears to be attenuated by menopause hormone therapy. This study extends the time frame for detectable changes and potential preventative care to almost a decade before menopause. More broadly, the present deconvolution approach can sharpen biological transitions from noisy, registry-scale data, a strategy transferable to other life-course events such as puberty, pregnancy and disease onset.

Online content

Any methods, additional references, Nature Portfolio reporting summaries, source data, extended data, supplementary information, acknowledgements, peer review information; details of author contributions and competing interests; and statements of data and code availability are available at <https://doi.org/10.1038/s41591-026-04614-0>.

References

- Ruth, K. S. et al. Genetic insights into biological mechanisms governing human ovarian ageing. *Nature* **596**, 393–397 (2021).
- Ambikairajah, A., Walsh, E. & Cherbuin, N. A review of menopause nomenclature. *Reprod. Health* **19**, 29 (2022).
- Davis, S. R., Pinkerton, J., Santoro, N. & Simoncini, T. Menopause—biology, consequences, supportive care, and therapeutic options. *Cell* **186**, 4038–4058 (2023).
- Tepper, P. G. et al. Trajectory clustering of estradiol and follicle-stimulating hormone during the menopausal transition among women in the Study of Women's Health across the Nation (SWAN). *J. Clin. Endocrinol. Metab.* **97**, 2872–2880 (2012).
- Randolph, J. F. Jr et al. Change in follicle-stimulating hormone and estradiol across the menopausal transition: effect of age at the final menstrual period. *J. Clin. Endocrinol. Metab.* **96**, 746–754 (2011).
- Chen, P., Li, B. & Ou-Yang, L. Role of estrogen receptors in health and disease. *Front. Endocrinol.* **13**, 839005 (2022).
- Biason-Lauber, A. & Lang-Muritano, M. Estrogens: two nuclear receptors, multiple possibilities. *Mol. Cell. Endocrinol.* **554**, 111710 (2022).
- Kasarinaitė, A., Sinton, M., Saunders, P. T. K. & Hay, D. C. The influence of sex hormones in liver function and disease. *Cells* **12**, 1604 (2023).
- Samargandy, S. et al. Arterial stiffness accelerates within 1 year of the final menstrual period: the SWAN heart study. *Arterioscler. Thromb. Vasc. Biol.* **40**, 1001–1008 (2020).
- Samargandy, S. et al. Abdominal visceral adipose tissue over the menopause transition and carotid atherosclerosis: the SWAN heart study. *Menopause* **28**, 626–633 (2021).
- Neer, R. M. Bone loss across the menopausal transition. *Ann. N. Y. Acad. Sci.* **1192**, 66–71 (2010).
- Bromberger, J. T. et al. Major depression during and after the menopausal transition: Study of Women's Health Across the Nation (SWAN). *Psychol. Med.* **41**, 1879–1888 (2011).
- Mrowiec, K. et al. Association of serum metabolome profile with the risk of breast cancer in participants of the HUNT2 study. *Front. Oncol.* **13**, 1116806 (2023).
- Richardson, W. H. Bayesian-based iterative method of image restoration. *J. Opt. Soc. Am.* **62**, 55–59 (1972).
- Cohen, N. M. et al. Personalized lab test models to quantify disease potentials in healthy individuals. *Nat. Med.* **27**, 1582–1591 (2021).
- Bar, A. et al. Pregnancy and postpartum dynamics revealed by millions of lab tests. *Sci. Adv.* **11**, eadr7922 (2025).
- Collaborative Group on Hormonal Factors in Breast Cancer. Menarche, menopause, and breast cancer risk: individual participant meta-analysis, including 118,964 women with breast cancer from 117 epidemiological studies. *Lancet Oncol.* **13**, 1141–1151 (2012).
- Schoenaker, D. A. J. M., Jackson, C. A., Rowlands, J. V. & Mishra, G. D. Socioeconomic position, lifestyle factors and age at natural menopause: a systematic review and meta-analyses of studies across six continents. *Int. J. Epidemiol.* **43**, 1542–1562 (2014).
- Jian, J., Pelle, E. & Huang, X. Iron and menopause: does increased iron affect the health of postmenopausal women? *Antioxid. Redox Signal.* **11**, 2939–2943 (2009).
- Ho, D. E., Imai, K., King, G. & Stuart, E. A. MatchIt: nonparametric preprocessing for parametric causal inference. *J. Stat. Softw.* **42**, 1–28 (2011).
- Harlow, S. D. et al. Executive summary of the Stages of Reproductive Aging Workshop + 10: addressing the unfinished agenda of staging reproductive aging: addressing the unfinished agenda of staging reproductive aging. *Menopause* **19**, 387–395 (2012).
- Bull, J. R. et al. Real-world menstrual cycle characteristics of more than 600,000 menstrual cycles. *NPJ Digit. Med.* **2**, 83 (2019).
- Khosla, S., Oursler, M. J. & Monroe, D. G. Estrogen and the skeleton. *Trends Endocrinol. Metab.* **23**, 576–581 (2012).
- Stachenfeld, N. S. Hormonal changes during menopause and the impact on fluid regulation. *Reprod. Sci.* **21**, 555–561 (2014).
- Vahter, M., Berglund, M. & Akesson, A. Toxic metals and the menopause. *J. Br. Menopause Soc.* **10**, 60–64 (2004).
- Santin, A. P. & Furlanetto, T. W. Role of estrogen in thyroid function and growth regulation. *J. Thyroid Res.* **2011**, 875125 (2011).
- Nordin, B. E. C. et al. A longitudinal study of bone-related biochemical changes at the menopause. *Clin. Endocrinol.* **61**, 123–130 (2004).
- Wilson, S. M. C., Bivins, B. N., Russell, K. A. & Bailey, L. B. Oral contraceptive use: impact on folate, vitamin B6, and vitamin B12 status. *Nutr. Rev.* **69**, 572–583 (2011).

29. Scarabin, P.-Y. et al. Effects of oral and transdermal estrogen/progesterone regimens on blood coagulation and fibrinolysis in postmenopausal women: a randomized controlled trial. *Arterioscler. Thromb. Vasc. Biol.* **17**, 3071–3078 (1997).
30. Li, J. et al. Prevalence and associated factors of depression in postmenopausal women: a systematic review and meta-analysis. *BMC Psychiatry* **24**, 431 (2024).
31. Shifren, J. L. et al. A comparison of the short-term effects of oral conjugated equine estrogens versus transdermal estradiol on C-reactive protein, other serum markers of inflammation, and other hepatic proteins in naturally menopausal women. *J. Clin. Endocrinol. Metab.* **93**, 1702–1710 (2008).
32. Vongpatanasin, W. et al. Differential effects of oral versus transdermal estrogen replacement therapy on C-reactive protein in postmenopausal women. *J. Am. Coll. Cardiol.* **41**, 1358–1363 (2003).
33. Trenti, A. et al. Estrogen, angiogenesis, immunity and cell metabolism: solving the puzzle. *Int. J. Mol. Sci.* **19**, 859 (2018).
34. Georgiadou, P. & Sbarouni, E. Effect of hormone replacement therapy on inflammatory biomarkers. *Adv. Clin. Chem.* **47**, 59–93 (2009).

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Methods

Ethics approval

This study complies with all relevant ethical regulations. The use of the Clalit Health Services dataset was approved by the Clalit Helsinki Committee (RMC-1059-20). We used public data from NHANES that was conducted under approval of the National Center for Health Statistics Research Ethics Review Board. The present study analyzed existing de-identified data, and participants received no compensation from the investigators. Sex was considered in the study design because menopause is a female-specific biological process, with male individuals included as comparison controls. Sex was recorded by the source datasets (self-reported in NHANES and recorded in the Clalit electronic medical record); gender identity was not available.

Data and cohorts

We analyzed two datasets originating from the USA (NHANES) and Israel (Clalit). NHANES is a cross-sectional health study that has been collected every 2 years from 1999 to 2022 that includes laboratory tests, health questions, exams and outcomes³⁵. Clalit is a large electronic medical record (all-comers) longitudinal dataset that includes about half the Israeli population¹⁵. We analyzed healthy laboratory test data that excluded data points with the confounding effects of medications or disease¹⁵, resulting in 1.3 million eligible female individuals aged 30–70 from years 2004–2024.

Eligibility criteria

Clalit. We analyzed all comers aged 30–70 from years 2004–2024. We excluded pregnant female individuals ($N = 173,000$).

NHANES. We analyzed 12 biennial waves from 1999 to 2022. We excluded pregnant female individuals ($N = 1,326$). For MHT comparison (Fig. 3), we only analyzed female individuals from survey years 1999 to 2019 (2022 had no MHT data owing to coronavirus disease 2019 (COVID-19)), with all covariates needed for matching: menopause status, age, poverty income ratio, smoker status, insurance status, diabetes status, ethnicity and education, with final $N = 738$ MHT users.

Variable definitions

Menopause status (NHANES only). We included all nonpregnant female individuals regardless of the reason for menopause (in sensitivity analysis, we restricted to natural menopause at typical ages, showing highly concordant results with Pearson's $r = 0.97$; Supplementary Fig. 7). Menopause status (female individuals only) was determined from the clinical definition of 12 months without period² together with supplemental information to confirm status. We used two questions, the first is: have you 'had regular/at least one period in the past 12 months?'. The second follow-up question is 'what is the reason (for no periods)?', where we require the individual to specify 'menopause' as the reason. Individuals that reported having periods were defined as nonmenopausal (RHQ030/RHQ031, regular periods/at least one period in the last 12 months). Individuals were further classified as follows. Those self-reporting not having periods were classified as nonmenopausal if self-reported pregnant (this year or previous) or breastfeeding, whereas individuals who self-reported menopause were classified as menopausal (RHQ040/RHD042/RHD043, reason not having regular periods); individuals that reported any other reason for not having periods were classified as unknown (NA, not available) menopause status. RHD042 did not differentiate menopause from hysterectomy as the reason for not having regular periods but these cases were corrected afterwards as follows. We reclassified all female individuals who had a hysterectomy that reported having either a single ovary or no ovaries removed as unknown (NA) menopause age and status, because the hysterectomy would prevent them from having periods (RHQ300/RHQ305/RHQ310/RHQ320); female individuals who reported their menopause age before their hysterectomy age (RHQ291) were still

included. We included participants taking oral contraceptives. Some of these individuals may not have periods, in which case, they were classified as unknown menopausal status. Finally, some individuals with indeterminate menopause status were classified according to age as follows: nonresponders to regular periods (RHQ030/RHQ031) under the age of 30 were classified as nonmenopausal, and responders over the age of 60 who reported not having regular periods were classified as menopausal (justified by the observed statistics that showed 98.3% of female individuals are nonmenopausal at age 30 and only 0.9% of female individuals were nonmenopausal at age 60). Self-reported age of menopause is top-coded at 60 in NHANES, which was extrapolated using survival modeling³⁶ as described in the 'YoGlen method 1 for NHANES data' section. Clalit did not have menstrual data, so menstrual status was not used for that dataset. Male individuals and the 26.8% of female individuals with unknown menopause status were imputed with a menopause age using the YoGlen algorithm described later in the methods section. We performed sensitivity analysis to consider the effects of unknown menopause status, hysterectomy and early/late menopause in Supplementary Fig. 7, which shows nearly perfect concordance of results, $r = 0.97$, between a restricted age range of 45–53 years with known menopause status and our reported FMP jump sizes.

MHT

NHANES. We considered female individuals as currently taking MHT if they had known postmenopause status and either (1) self-reported taking MHT or (2) reported taking any drugs containing estrogens (full list in Supplementary Table 3). For (1), we gated NHANES using RHQ540 (ever used female hormones excluding birth control): any participant reporting 'no' was classified as no MHT. Affirmative to any of the following was classified as yes MHT: RHQ558 (taking estrogen-only pills now; 2.9% of female individuals), RHQ566 (taking progestin-only pills now; 0.2% of female individuals), or RHQ574 (taking combination pill now; 1.1% of female individuals). After 2012, NHANES stopped asking specific questions regarding MHT usage. For (2), we used the RQQ_RX prescription drug files from each year except 2022 (not reported). We included the following types of estrogen-containing drug classes as MHT: all 'E2', estropipate, mestranol, all 'estrogen', as well as nine individuals using progesterone-only MHT.

Clalit. In Clalit, menopausal status is not recorded. We therefore defined MHT users as female individuals aged 45–55 who were prescribed at least twice the MHT drugs Angeliq (drospirenone 2 mg–estradiol hemihydrate 1 mg) or Eviana (estradiol hemihydrate 0.5 mg–norethisterone acetate 0.1 mg). We matched these individual users with controls from the same clinic, age and birth year. For each laboratory test and each group, we defined the menopause change Δ as the mean of the postmenopausal window (ages 54–60) minus the corresponding mean in the premenopausal window (ages 42–48). Δ MHT is the mean menopause change for MHT patients, and Δ control is the mean menopause change for the control group. MHT attenuation is defined as the relative reduction in the menopause change of MHT users compared with their matched controls: $1 - (\Delta$ MHT/ Δ control).

Variables and outcomes

We analyzed 90 laboratory blood tests and 31 outcomes for their time dependence with respect to inferred time of FMP. We group by systems as described in Extended Data Table 1 and Supplementary Table 2. Blood tests describe bone, liver, kidney, immune and other systems. Outcomes include signs, symptoms and diagnoses.

Preprocessing

Clalit and NHANES. All laboratory values were log-scaled and standardized to sex-specific mean and s.d. using the control reference age range of 25–45 (datasets were standardized separately). An outlier

cutoff was applied at ± 5 s.d. ($<0.3\%$ of data points). Log laboratory value distributions resembled normal distributions.

Clalit. Laboratory values were filtered to exclude measurements from nonhealthy individuals and from individuals taking medications that affect each specific laboratory test. To do so, we used the dataset described by Cohen et al.¹⁵, which excluded 131 chronic conditions and 5,223 drug–test pairs. Pregnancies were excluded separately. Body mass index (BMI) was linked cross-sectionally for the healthy population using the most recent measurement within the study period, and reported as median (IQR). Bootstrapping on Clalit was performed by grouping individuals by year of test date and sampling the 20 years with replacement. Test values of zero were removed ($<0.3\%$ of data points; Extended Data Table 2).

The YoGlen algorithm

We estimate the unknown age of FMP using a latent variable model³⁷ with appropriate approximations. Let p denote an arbitrary probability density function, a_m is the unknown age of FMP, m is the binary menopause status variable (available in NHANES but not Clalit), a is the known age, and y is a vector of known laboratory test values. The two results we derive are (1) how to estimate the distribution of the unknown age of FMP of each individual, $p(a_m|y, a)$ using the observed data and (2) how to estimate mean cross-sectional laboratory trajectories as a function of the unknown time to FMP, $E[y_j|a]$. Jump size was estimated using resampled regression model predictions. For method 1, we used ten-repeat, tenfold cross-validation. For method 2, we used bootstrapping of $E[y_j|a]$.

YoGlen method 1 for NHANES data

To estimate the unknown FMP time, $p(a_m|y, a)$ we use Bayes' theorem $p(a_m|y, a, m) \propto p(a_m|a, m)p(y|a_m, a, m)$. We observed on the basis of comparison to SWAN data (Extended Data Fig. 5) that a good approximation was to use only the lowest-order term $p(a_m|y, a, m) \approx p(a_m|a, m)$. We used draws from $p(a_m|a, m)$ to impute the unknown a_m , where $p(a_m)$ is the reference menopause age distribution from NHANES (Fig. 1), estimated by modeling the log-hazard as a ten-knot natural spline³⁶. Female individuals with double oophorectomies (12%) were drawn separately using their own distribution. For female individuals where menopause status m is known (73.2%), conditioning on a and m restricts the permitted a_m to be before current age if nonmenopausal and after current age if menopausal. We used a discrete grid to consider all possible a_m from 20–70 at 1 year resolution. Once the $p(a_m|a, m)$ grid is estimated for each individual, we use it to draw 15 possible a_m for each individual, creating 15 completed datasets that are analyzed in parallel, and then, the results are pooled using Rubin's rules³⁸ to account for the uncertainty in a_m .

In NHANES, most (89%) of the self-reported postmenopausal female individuals also included their age of menopause. Prior research indicates that self-reported age of menopause is accurate to about 1 year³⁹, and hence, the age of FMP for these participants was estimated assuming $p(a_m)$ was a normally distributed true age of menopause with mean equal to their reported value and a 1-year s.d. Validation by comparison with longitudinal data from SWAN demonstrates that YoGlen fits well to the population mean for the key variables available in SWAN, FSH and E2, when only age and menstrual status are included (Extended Data Fig. 5). Inclusion of FSH and E2 into the model tended to fit worse (not shown), ostensibly because of the strong heteroscedasticity due to fluctuations in sex hormones that occurs during perimenopause^{21,40} and suddenness of the transition. Therefore for NHANES the overall population trends were estimated using only menstrual status and age.

YoGlen method 2 for Clalit data

For Clalit, we did not have access to menstrual status data, precluding using YoGlen method 1, so we instead used a regression model to deconvolve each laboratory test to convert the age-dependent cross-sectional

means into time-since-FMP dependent dynamics, effectively using $p(a_m|y_j, a, m) \propto p(a_m|a)p(y_j|a_m, a)$. We modeled each laboratory test as piecewise linear,

$$f(t|a) \equiv \beta_0 + \alpha_0 t + (\beta_m + \alpha_m t) \times I(t > 0) + \sum_{i=1}^p (\alpha_i \times (t - t_i) \times I(t > t_i)),$$

where $t \equiv a - a_m$ is the time to menopause, I is the indicator function (1 when true, 0 otherwise), p is the number of change points ($p = 1$ for Fig. 4 and $p = 0$ otherwise), and α_i and β_i are the regression model parameters. The β_m parameter permits a jump at FMP ($t = 0$). Averaging this equation over age of menopause a_m yields the cross-section mean as function of age that was fitted using least squares regression on the age-binned average values

$$E[y|a] = \beta_0 + \alpha_0 E[t|a] + \beta_m C_m(a) + \alpha_m \int_0^a C_m(a_m) da_m + \sum_{i=1}^p \alpha_i \int_0^{\max(0, a-t_i)} C_m(a_m) da_m,$$

where $E[t|a] = a - E[a_m]$, $E[a_m]$ is the average FMP age, and C_m is the cumulative density of the FMP; these values were computed numerically from a published menopause age distribution from 306,068 healthy female individuals¹⁷. For the change-point results (Fig. 4), we considered all possible $t_i < 0$ (premenopause) and selected the best location for the change point (t_i) on the basis of the lowest Bayesian information criterion.

Why do we call YoGlen a deconvolution, and what is the relationship to latent variable modeling?

Our latent variable is the unknown age of menopause a_m , which we seek to infer from a proxy (age, a) so that we can understand its relationship with the observed laboratory value y . This is akin to the problem of deblurring an image where $y(a - a_m)$ is the true image and $y(a)$ is the distorted image observed through the lens. We do not know the latent variable, so we have to invert what we do know, which is

$$p(y|a) = \int_{-\infty}^{\infty} p_1(y, a_m, a) p_2(a_m|a) da_m.$$

In our case, y depends on the time to FMP

$$p(y|a) = \int_{-\infty}^{\infty} p_1(y|a - a_m) p_2(a_m|a) da_m = p_2 * p_1,$$

a convolution of functions p_2 and p_1 over the latent variable, a_m . YoGlen solves the inverse problem to find $p_1(y|a - a_m)$ based on the observed $p(y|a)$ and reference $p_2(a_m|a)$. YoGlen is thus a process of deconvolution, as it is the inverse of convolution.

Propensity score matching. Propensity score matching was used to match MHT recipients after menopause to controls both before and after menopause (1:1 matching ratio). Propensity score matches each individual to similar controls using logistic regression on a set of covariates to determine similarity²⁰. For controls, we matched to: age, poverty income ratio >1 (yes/no), smoker status (smokes now/does not), insurance status (has/does not), diabetes status (positive/negative), age of menopause, survey year ≥ 2005 (binary), black ethnicity (yes/no) and education $\geq$ 'some college' (yes/no). Black ethnicity was included as the black female cohort had higher BMD than non-black (U test $P = 10^{-16}$, mean difference: 0.75 ± 0.02 z-score total BMD). The score balance was determined both visually using absolute mean difference and Kolmogorov–Smirnov statistic threshold of 0.1 (ref. 41).

All covariates were balanced in the aftermenopause control group, but age differed in the before-menopause control. The premenopause control group differed by their median (IQR) of 51 years (48–53 years) versus 61 years (54–67 years) for the MHT group; this was expected and tolerated because the MHT users are usually postmenopausal and therefore typically older.

Regression fit lines. The regression lines in Figs. 1, 2, 4 and 5 were computed using model averages weighted by repeated cross-validation. To do so, we performed model selection (models listed below) using tenfold, ten-repeat cross-validation. We used the out-of-sample mean-squared error to choose continuous models, and area under the receiver operating characteristic curve⁴² to choose binomial models. Each fold included fitting the model to each of the FMP age estimates from YoGlen, then pooling using Rubin's rules³⁸; pooled individual predictions were used to compute the error. In Figs. 1 and 2, we present the model average where we picked one of four Gaussian regression models at each repeat (ten-knot spline, ten-knot spline with jump, ten-knot location-scale or piecewise ten-knot location-scale) and then aggregated grid predictions from –25 to 25 years-to-FMP over the 100 total repeats. The location-scale models included joint prediction of mean and variance to mitigate issues with heteroskedasticity, probably originating from late menopause transition fluctuations²¹ (for example, Fig. 4g–i). Similarly, in Fig. 5, we present the model average where we picked one of two weighted binomial regression models at each repeat, because the outcome variables are binary and location-scale models are therefore not relevant (ten-knot spline, ten-knot spline with jump). Rare outcomes risk underfitting, and therefore, we set binomial case weights to 1 for the majority outcome and majority/minority ratio for minority outcome⁴³. In Fig. 4, we present data for female individuals with known nonmenopausal status and therefore did not require model selection. We present the ten-knot Gaussian location-scale model, which allows estimates of s.d. Best-fit lines used the `mgcv` package in R⁴⁴. In the analysis of MHT (Fig. 3), we used linear regression on data pooled using Rubin's rules owing to the relatively small number of data points.

Statistics. Statistics were performed in R v4.5.1 (NHANES) and Python v3.9.23 (Clalit). All error bars/bands are standard errors. Correlations are Pearson's. All tests are two-sided. Significance was set at $P < 0.05$. FDR correction used the Benjamini–Hochberg algorithm⁴⁵.

All methods are available on GitHub (<https://github.com/AlonLabWIS/YoGlen>).

Reporting summary

Further information on research design is available in the Nature Portfolio Reporting Summary linked to this article.

Data availability

Aggregated and simulated data are available via GitHub at <https://github.com/AlonLabWIS/YoGlen>. Individualized data for NHANES are available via GitHub at <https://www.cdc.gov/nchs/nhanes/>. Individualized data from Clalit are not publicly available. Quantiles for the Clalit data used are available at <https://tanaylab.weizmann.ac.il/labs/>. Source data are provided with this paper.

Code availability

All analysis code is available via GitHub at <https://github.com/AlonLabWIS/YoGlen>.

References

35. Centers for Disease Control and Prevention (CDC), National Center for Health Statistics (NCHS) *National Health and Nutrition Examination Survey Data* <https://www.cdc.gov/nchs/nhanes/index.html> (US Department of Health and Human Services, Centers for Disease Control and Prevention, accessed 2026).

36. Fauvermier, M., Remontet, L., Uhry, Z., Bossard, N. & Roche, L. *survPen*: an R package for hazard and excess hazard modelling with multi-dimensional penalized splines. *J. Open Source Softw.* **4**, 1434 (2019).
37. Bartholomew, D., Knott, M. & Moustaki, I. *Latent Variable Models and Factor Analysis: A Unified Approach* (Wiley, 2011).
38. Murray, J. S. Multiple imputation: a review of practical and theoretical findings. *Stat. Sci.* **33**, 142–159 (2018).
39. den Tonkelaar, I. Validity and reproducibility of self-reported age at menopause in women participating in the DOM-project. *Maturitas* **27**, 117–123 (1997).
40. Greene, D. N. et al. A comprehensive review of estradiol, progesterone, luteinizing hormone, and follicle-stimulating hormone in the context of laboratory medicine to support women's health. *Clin. Chem.* **71**, 842–857 (2025).
41. Greifer, N. *cobalt*: covariate balance tables and plots. CRAN <https://doi.org/10.32614/CRAN.package.cobalt> (2025).
42. Robin, X. et al. pROC: an open-source package for R and S+ to analyze and compare ROC curves. *BMC Bioinformatics* **12**, 77 (2011).
43. Pridham, G., Rockwood, K. & Rutenber, A. Efficient representations of binarized health deficit data: the frailty index and beyond. *Geroscience* **45**, 1687–1711 (2023).
44. Wood, S. N. Fast stable restricted maximum likelihood and marginal likelihood estimation of semiparametric generalized linear models. *J. R. Stat. Soc. B* **73**, 3–36 (2011).
45. Benjamini, Y. & Hochberg, Y. Controlling the false discovery rate: A practical and powerful approach to multiple testing. *J. R. Stat. Soc. B* **57**, 289–300 (1995).
46. Colditz, G. A. et al. Reproducibility and validity of self-reported menopausal status in a prospective cohort study. *Am. J. Epidemiol.* **126**, 319–325 (1987).
47. Collaborative Group on Hormonal Factors in Breast Cancer Type and timing of menopausal hormone therapy and breast cancer risk: individual participant meta-analysis of the worldwide epidemiological evidence. *Lancet* **394**, 1159–1168 (2019).

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Author contributions

All authors reviewed the paper before submission. Conceptualization: U.A., G.P., N.L.-S., M.N., N.H. and Y.T. Methodology: U.A., G.P., Y.H., N.H. and Y.T. Formal analysis: Y.H. and G.P. Funding acquisition: U.A. Visualization: Y.H., G.P. and U.A. Supervision: U.A. and N.L.-S. Writing: U.A., G.P. and Y.H.

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Competing interests

The authors declare no competing interests.

Additional information

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Extended Data Table 1 | Lab tests for NHANES (females)

Lab test	Short name	System	N obs	N outliers dropped ^{a,c}	Position ^a	Scale ^a	epsilon ^a	NHANES code	Units	N males
17 β -hydroxyprogesterone	17-ohp	gonad	3009	0	0.389	1.052	0	LBD17HSI	nmol/L	5878
albumin	albumin	liver	29439	13	3.706	0.102	0	LBDSALSI	g/L	29931
alkaline phosphatase	alp	liver	26978	13	4.139	0.333	0	LBXSAPSI	U/L	27673
alanine aminotransferase	alt	liver	29395	42	2.875	0.464	0	LBXSATSI	U/L	29866
anti-mullerian hormone	amh	gonad	3054	0	2.092	1.373	0	LBDAMHSI	pmol/L	2515
androstenedione	andro	gonad	3053	1	1.209	0.496	0	LBDANDSI	nmol/L	5893
apolipoprotein	apob	lipid metabolism	7621	2	-0.168	0.289	0	LBDAPBSI	g/L	7153
aspartate aminotransferase	ast	liver	29375	107	3.003	0.33	0	LBXSASSI	U/L	29829
vitamin b12	b12	micronutrients	14530	34	5.857	0.51	0	LBDB12SI	pmol/L	13417
beta-2 microglobulin	b2m	kidney	6451	20	0.523	0.219	0	SSB2M	mg/L	5933
bicarbonate	bicarb	kidney	29401	9	3.165	0.095	0	LBXSC3SI	mmol/L	29875
bilirubin (total)	bilirubin	liver	26966	21	-0.724	0.517	0.01	LBXSTB	mg/dL	27666
body mass index	bmi	glucose metabolism	34280	0	3.354	0.253	0	BMXBMI	kg/m ²	31401
nt-probnp	bnp	heart	6423	2	3.759	0.837	0	SSBNP	pg/ml	5887
bone alkaline phosphatase	bone alp	bone	3374	0	2.539	0.391	0	LBXBAP	ug/L	3017
blood urea nitrogen	bun	kidney	29431	6	2.302	0.355	0	LBXSBU	mg/dL	29920
calcium (total)	calcium	bone	29422	18	0.838	0.039	0	LBDSCASI	mmol/L	29910
creatine phosphokinase	ck	muscle	14538	18	4.53	0.558	0	LBXSCK	IU/L	16053
cobalt	cobalt	metal	6459	21	1.217	0.637	0	LBDBCOSI	nmol/L	6165
c-peptide	c-peptide	glucose metabolism	3386	4	-0.378	0.478	0	LBXCPSI	nmol/L	3083
c-reactive protein	crp	inflammation	15019	0	-1.443	1.354	0	LBXCRP	mg/dL	13905
cystatin c	cystatin	kidney	6455	23	-0.42	0.199	0	SSCYST	mg/L	5940
dehydroepiandrosterone sulfate	dhea	gonad	3030	2	1.01	0.631	0	LBDDHESI	Åmol/L	2442
estrone	e1	gonad	3041	6	5.48	0.83	0	LBDESOSI	pmol/L	5786
estradiol	e2	gonad	8298	0	4.188	1.247	0	LBXEST	pg/mL	10725
eosinophils number	eosinophils	wbc	33115	22	-1.373	0.435	0.1	LBDEONO	count	30386
glucose (plasma, fasting)	f glucose	glucose metabolism	16343	104	4.565	0.183	0	LBXGLU	mg/dL	14951
femoral neck bone mineral density	femor neck bmd	bone mass	10767	2	-0.157	0.15	0	DXXNKBMD	gm/cm ²	11463
ferritin	ferritin	iron	19452	0	3.57	0.982	0	LBDFERSI	ug/L	10445
fibrinogen	fibrinogen	clotting	2862	2	1.259	0.214	0	LBDFBSI	g/L	2828
folate (serum, total)	folate	micronutrients	15918	3	2.69	0.546	0	LBDFOT	ng/mL	13127
folate (rbc)	folate (rbc)	micronutrients	16067	1	6.113	0.396	0	LBDRFO	ng/mL	13223
follicle stimulating hormone	fsh	gonad	4826	0	1.685	1.07	0	LBXFSH	mIU/mL	5867
triiodothyronine (T3, free)	ft3	thyroid	4447	11	1.145	0.149	0	LBXT3F	pg/mL	4325
thyroxine (T4, free)	ft4	thyroid	4449	12	2.291	0.199	0	LBdT4FSI	pmol/L	4330
gamma glutamyl transferase	ggt	liver	29434	38	2.819	0.601	0	LBXSGTSI	U/L	29915
glycohemoglobin	hba1c	glucose metabolism	33179	188	1.676	0.119	0	LBXGH	%	30408
glucose tolerance test (2 hour)	gtt	glucose metabolism	5482	0	1.751	0.324	0	LBDGLTSI	mmol/L	5382
high-density lipoprotein (direct)	hdl	lipid metabolism	27902	3	0.348	0.276	0	LBHDHDSI	mmol/L	25850
hematocrit	hematocrit	rbc	25111	34	3.651	0.093	0	LBXHCT	%	22953
hemoglobin	hemoglobin	iron	33239	71	2.566	0.105	0	LBXHGB	g/dL	30430
homocysteine	homocysteine	kidney	6903	3	1.782	0.339	0	LBXHCY	umol/L	6288
high sensitivity c-reactive protein	hsrnp	inflammation	12347	0	0.766	1.296	0	LBXHSCRNP	mg/L	11153
insulin	insulin	glucose metabolism	15945	7	2.27	0.721	0	LBXIN	uU/mL	14657
iron	iron	iron	29416	3	2.489	0.542	0	LBDSIRSI	umol/L	29904
l1 bone mineral density	l1 bmd	bone mass	10901	2	-0.036	0.138	0	DXXL1BMD	gm/cm ²	10815

Extended Data Table 1 (continued) | Lab tests for NHANES (females)

Lab test	Short name	System	N obs	N outliers dropped ^{a,c}	Position ^a	Scale ^a	epsilon ^a	NHANES code	Units	N males
l2 bone mineral density	l2 bmd	bone mass	10502	1	0.065	0.126	0	DXXL2BMD	gm/cm^2	10401
l3 bone mineral density	l3 bmd	bone mass	10537	0	0.095	0.121	0	DXXL3BMD	gm/cm^2	9895
l4 bone mineral density	l4 bmd	bone mass	9965	1	0.083	0.12	0	DXXL4BMD	gm/cm^2	9466
lactate dehydrogenase	ldh	muscle	26852	20	4.834	0.21	0	LBXSLDSI	U/L	26802
low-density lipoprotein	ldl	lipid metabolism	13928	4	1.001	0.305	0	LBDLDLSI	mmol/L	14127
lead	lead	metal	30427	3	-3.234	0.623	0.002	LBDBPBSI	umol/L	27936
luteinizing hormone	lh	gonad	3054	0	1.697	1.185	0	LBXLUH	mIU/mL	5882
lymphocyte number	lymphocytes	wbc	33115	17	0.763	0.305	0	LBDLYMNO	count	30386
mean arterial pressure ^a	map	heart	25626	3	4.421	0.125	0	bpd-pp/3	mmHg	24096
mean cell volume	mcv	rbc	33239	98	4.471	0.079	0	LBXMCVSI	fL	30430
monocyte number	monocytes	wbc	33115	11	-0.505	0.276	0.1	LBDMONO	count	30386
segmented neutrophils number	neutrophils	wbc	33115	9	1.449	0.405	0	LBDNENO	count	30386
serum neurofilament light chain	nfl	cognition	1081	1	2.248	0.584	0	SSSNFL	pg/ml	990
osmolality	osmolality	kidney	29431	20	5.62	0.017	0	LBXSOSI	mOsm/kg	29916
oxychlordane	oxychlordane	pop	2063	0	-3.018	0.713	0	LBXOXY	ng/g	1815
pcb074	pcb074	pop	2169	0	-3.494	0.628	0	LBX074	ng/g	1933
phosphorus	phosphate	bone	29431	3	0.17	0.151	0	LBDSPHSI	mmol/L	29916
platelet count	platelets	clotting	33238	42	5.585	0.257	0	LBXPLTSI	%	30430
potassium	potassium	kidney	29431	9	1.359	0.076	0	LBXSKSI	mmol/L	29886
pulse pressure	pp	heart	25626	1	3.747	0.249	0	sbp-dbp	mmHg	24096
progesterone	progesterone	gonad	3027	0	0.19	2.483	0	LBDPG4SI	nmol/L	5860
parathyroid hormone (Elecys method)	pth	bone	4626	0	3.566	0.497	0	LBXPT21	pg/mL	4322
red blood cell count	rbc	rbc	33239	15	1.484	0.089	0	LBXRBCSI	count	30430
red blood cell distribution width	rdw	rbc	33239	90	2.588	0.11	0	LBXRDW	%	30430
systolic blood pressure	sbp	heart	25767	0	4.72	0.115	0	BPXSY	mmHg	24205
creatinine (serum)	scr	kidney	29435	88	4.095	0.239	0	LBDSCRSI	umol/L	29919
selenium (blood)	selenium	metal	15255	26	5.216	0.13	0	LBXBSE	ug/L	13965
sex hormone binding globulin	shbg	liver	8083	0	4.109	0.695	0	LBXSHBG	nmol/L	10471
sodium	sodium	kidney	29439	26	4.932	0.016	0	LBXSNASI	mmol/L	29927
testosterone (total)	testo	gonad	10903	18	3.154	0.562	0	LBXTST	ng/dL	9923
thyroglobulin	thyroglobulin	thyroid	4445	0	2.314	1.121	0	LBDTGNSI	ug/L	4328
total iron binding capacity	tibc	iron	14416	3	4.18	0.189	0	LBDTIBSI	umol/L	10317
total bone mineral content	total bmc	bone mass	5481	0	7.653	0.153	0	DXDTOBMC	g	5419
total bone mineral density	total bmd	bone mass	5481	0	0.089	0.085	0	DXDTOBMD	g/cm^2	5419
cholesterol (total)	total chol	lipid metabolism	32547	5	5.225	0.201	0	LBXTC	mg/dL	30015
transferrin saturation	transferrin sat.	iron	12213	5	2.933	0.607	0	LBDPCT	%	8377
triglycerides	tri	lipid metabolism	29419	4	0.155	0.582	0	LBDSTRSI	mmol/L	29919
cardiac hs-troponin I (Abbott)	troponin	heart	6435	1	0.074	0.753	0.1	SSTNIA	ng/L	5904
thyroid stimulating hormone	tsh	thyroid	4448	18	0.329	0.837	0	LBXTSH1	uIU/mL	4331
triiodothyronine (T3, total)	tt3	thyroid	4448	2	0.574	0.294	0	LBDTT3SI	nmol/L	4328
thyroxine (T4, total)	tt4	thyroid	4441	5	2.071	0.206	0	LBXTT4	ug/dL	4304
albumin (urine)	u albumin	kidney	30747	31	2.094	1.212	0	URXUMA	ug/mL	31238
creatinine (urine)	u creatinine	kidney	30721	0	4.604	0.732	3	URXUCR	mg/dL	31231
white blood cell count	wbc	wbc	33238	10	1.987	0.296	0	LBXWBCSI	count	30430

^ay = (log(x+epsilon)-position)/scale where y is the preprocessed lab value and x is the raw value (position and scale are the position and s.d. of log(x+epsilon) over ages 25–45; epsilon is to avoid log(0), it is equal to the smallest non-zero value when zero values are present). ^b|y| > 5. Note that the name LBXHCT was recycled (from hematocrit to hydroxycotinine) for waves 2013–2014, 2015–2016 and 2017–2018, that were excluded from analysis.

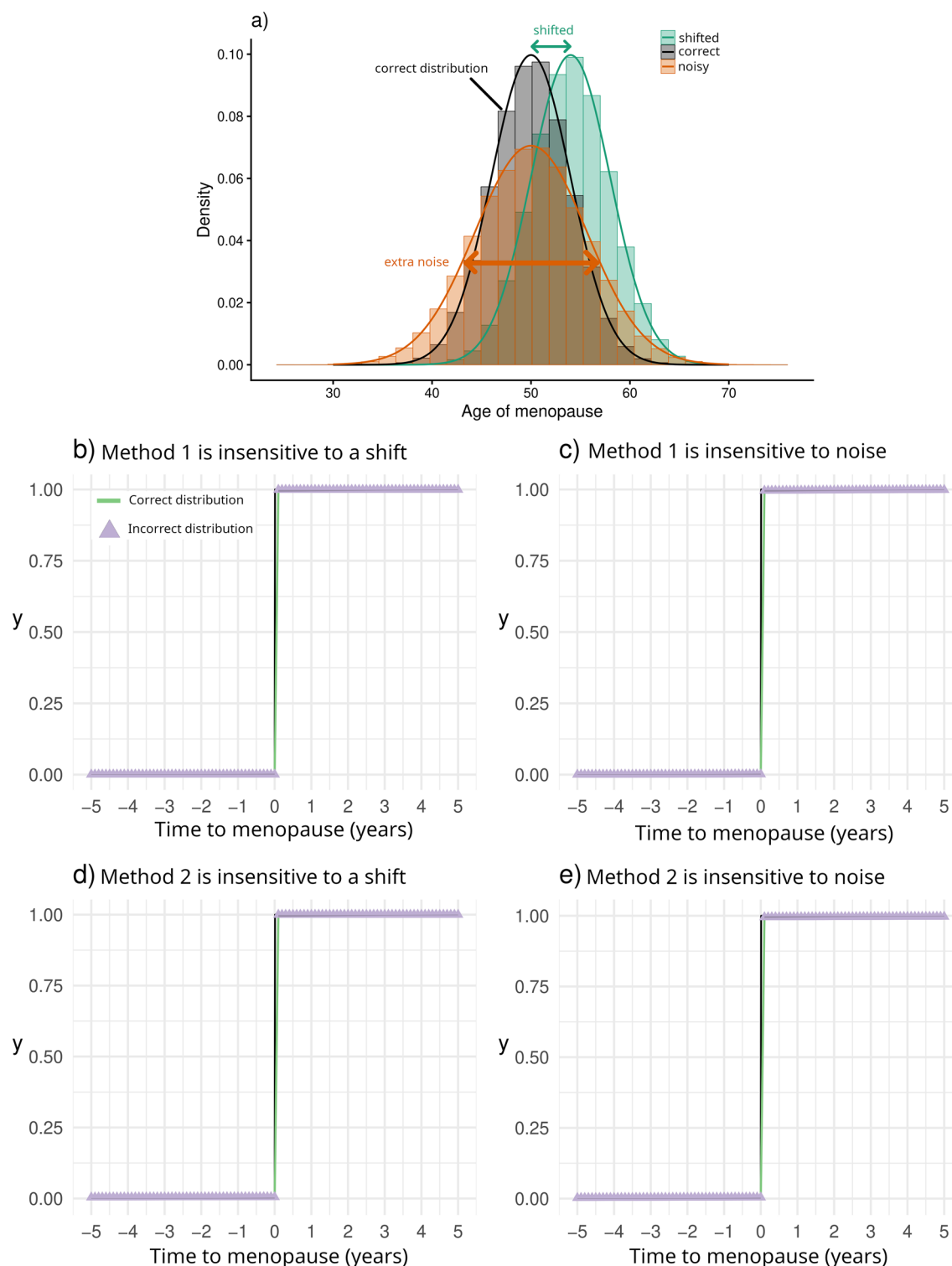
Extended Data Table 2 | Lab tests for Clalit (females)

Lab test	Short name	System	N obs	N outliers droppedâ€	Position ^a	Scale ^a	Units
fibrinogen	fibrinogen	clotting	116293	35	5.849	0.274	mg/dL
ferritin	ferritin	iron	1719306	703	3.147	0.968	ng/mL
iron	iron	iron	2449977	242	4.176	0.581	microg/dL
vitamin b12	b12	micronutrients	3023218	52	5.616	0.372	PMOL/L
folate (serum, total)	folate	micronutrients	1519186	121	2.833	0.495	nmol/L
albumin	albumin	liver	4172796	15308	1.44	0.081	g/dL
alanine aminotransferase	alt	liver	6685744	17790	2.728	0.517	units/L
aspartate aminotransferase	ast	liver	6682873	28430	2.929	0.342	units/L
bilirubin (total)	bilirubin	liver	4497469	6260	−0.695	0.457	mg/dL
gamma glutamyl transferase	ggt	liver	3118561	10286	2.816	0.606	IU/L
cholesterol (total)	total chol	lipid metabolism	6404325	1074	5.168	0.195	mg/dL
high-density lipoprotein (direct)	hdl	lipid metabolism	6028910	775	3.959	0.238	mg/dL
low-density lipoprotein	ldl	lipid metabolism	5934205	2006	4.612	0.282	mg/dL
glucose (plasma, fasting)	f glucose	glucose metabolism	7024278	31949	4.469	0.132	mg/dL
glycohemoglobin	hba1c	glucose metabolism	1101226	6581	1.673	0.087	percent
triglycerides	tri	lipid metabolism	6300450	1239	4.506	0.485	mg/dL
body mass index	bmi	glucose metabolism	1788096	735	3.257	0.24	kg/m2
insulin	insulin	glucose metabolism	16250	3	2.243	0.759	UIU/ML
creatine phosphokinase	ck	muscle	2067366	4576	4.274	0.534	IU/L
lactate dehydrogenase	ldh	muscle	3199192	5064	5.741	0.246	units/L
alkaline phosphatase	alp	liver	5732857	8959	4.16	0.32	units/L
phosphorus	phosphate	bone	3704081	4065	1.27	0.153	mg/dL
parathyroid hormone (Elecys method)	pth	bone	97325	49	3.7459	0.627	PG/ML
bicarbonate	bicarb	kidney	43232	99	3.191	0.147	mEq/L
sodium	sodium	kidney	6086346	3803	4.938	0.016	mEq/L
blood urea nitrogen	bun	kidney	6657666	4091	3.162	0.28	mg/dL
calcium (total)	calcium	bone	4591709	5222	2.226	0.046	mg/dL
creatinine (serum)	scr	kidney	7138400	7003	−0.418	0.187	mg/dL
creatinine (urine)	u creatinine	kidney	519270	116	4.743	0.667	mg/dL
potassium	potassium	kidney	328420	149	1.456	0.101	mEq/L
hematocrit	hematocrit	rbc	8299047	12623	3.642	0.099	percent
hemoglobin	hemoglobin	iron	8293168	18007	2.528	0.11	g/dL
mean cell volume	mcv	rbc	8306574	4986	4.443	0.085	pg/cell
red blood cell distribution width	rdw	rbc	7290162	17257	2.617	0.109	%
red blood cell count	rbc	rbc	8299961	11704	1.502	0.094	K-cells/ÅŽÅ¼L
thyroid stimulating hormone	tsh	thyroid	4771339	22247	0.595	0.61	mIU/l
triiodothyronine (T3, free)	ft3	thyroid	604217	4995	1.593	0.203	pmol/L
thyroxine (T4, free)	ft4	thyroid	1310752	6955	2.659	0.19	pmol/L
triiodothyronine (T3, total)	tt3	thyroid	142592	72	0.776	0.346	NMOL/L
thyroglobulin	thyroglobulin	thyroid	1562827	542	1.091	0.141	g/dL
monocyte number	monocytes	wbc	8066397	4923	−0.972	0.379	K-cells/ÅŽÅ¼L
white blood cell count	wbc	wbc	8299109	4029	1.902	0.305	K-cells/ÅŽÅ¼L
eosinophils number	eosinophils	wbc	8124619	100179	0.773	0.736	K-cells/ÅŽÅ¼L
lymphocyte number	lymphocytes	wbc	8096815	9345	0.716	0.337	K-cells/ÅŽÅ¼L
segmented neutrophils number	neutrophils	wbc	8101286	3567	1.338	0.409	1000/microL
estradiol	e2	gonad	1193933	12	6.23	1.18	pmol/L
follicle stimulating hormone	fsh	gonad	697924	193	2.031	0.778	IU/L
luteinizing hormone	lh	gonad	1057952	44	1.749	0.941	IU/L
progesterone	progesterone	gonad	808090	434	1.418	1.272	NMOL/L
androstenedione	andro	gonad	70776	9	1.754	0.595	NMOL/L
testosterone (total)	testo	gonad	282095	389	0.169	0.517	NMOL/L

Extended Data Table 2 (continued) | Lab tests for Clalit (females)

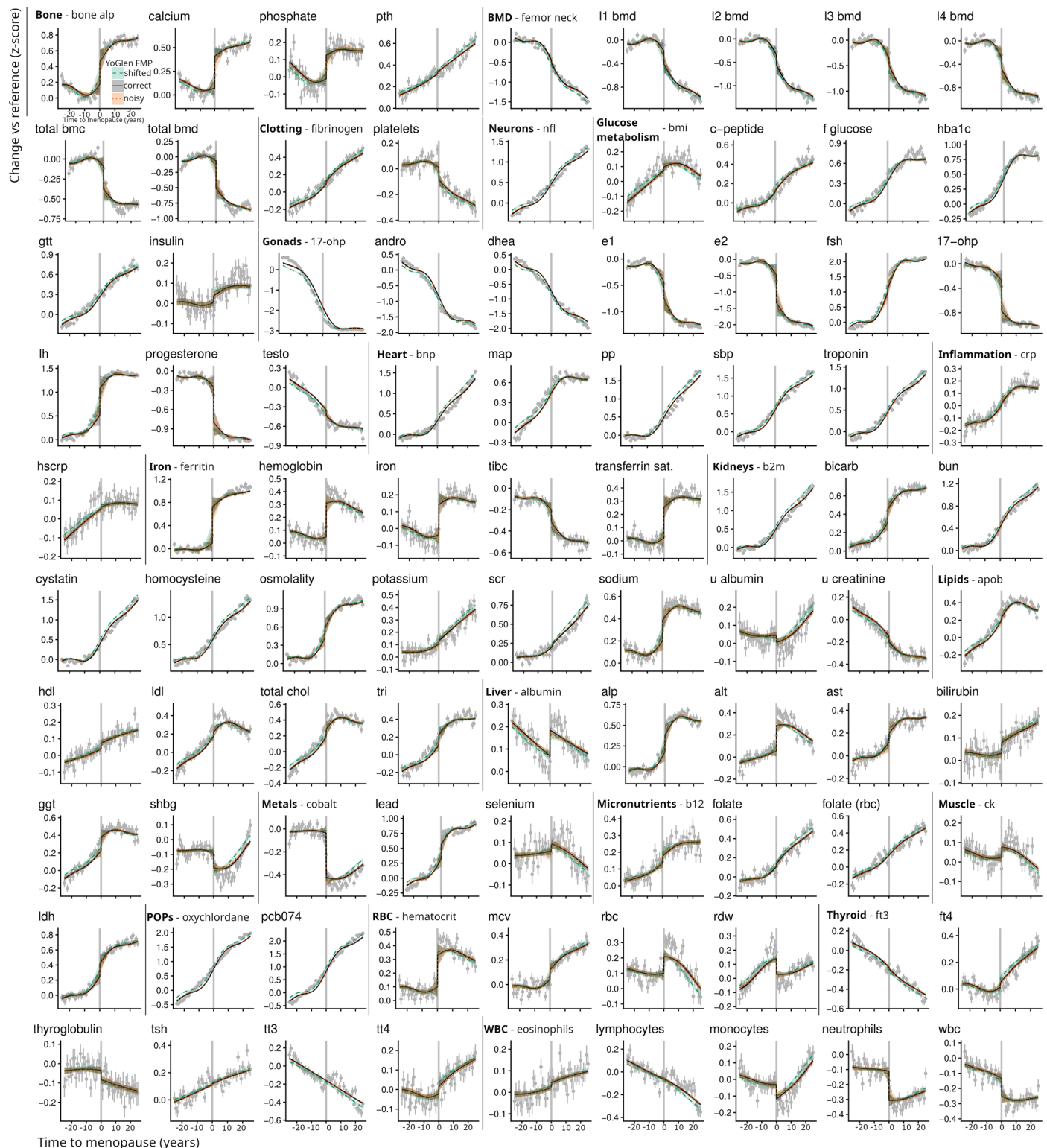
Lab test	Short name	System	N obs	N outliers dropped ^a	Position ^a	Scale ^a	Units
sex hormone binding globulin	shbg	liver	1562827	542	1.091	0.141	g/dL
c-reactive protein	crp	inflammation	1104572	10618	−0.939	1.386	mg/dL
17-hydroxyprogesterone	17-ohp	gonad	168142	193	0.946	0.735	NMOL/L
dehydroepiandrosterone sulfate	dhea	gonad	237437	28	1.314	0.57	UMOL/L
osmolality	osmolality	kidney	4903	20	5.66	0.043	mOsm/kg
platelet count	platelets	clotting	8290422	11552	5.555	0.27	K/microL

^a $y = (\log(x) - \text{position}) / \text{scale}$ where y is the preprocessed lab value and x is the raw value (position and scale are the position and s.d. of $\log(x)$ over ages 25–45). [†] $|y| > 5$. Values $x=0$ were also excluded from analysis.



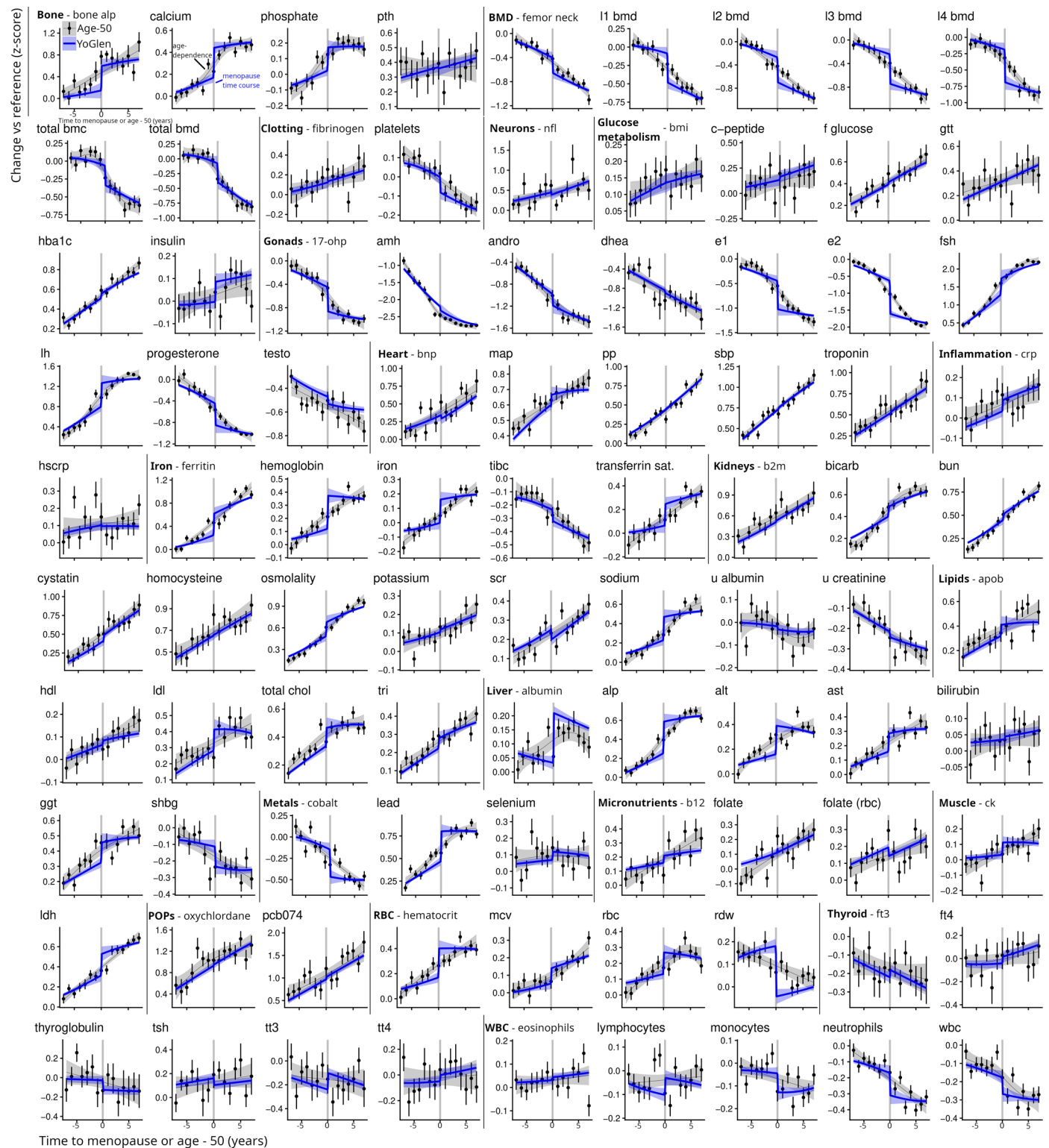
Extended Data Fig. 1 | The YoGlen method is insensitive to variations in the FMP distribution. Simulated data was a step function at $t = 0$ convolved with a normal FMP distribution $N(m_0, s_0)$ with $m_0 = 50$ years and $s_0 = 4$ years, $n = 10^5$. **a)** Original reference FMP distribution (black) and perturbed distributions: one that is shifted by 4 years (green, $m = m_0 + 4$) (differences between mean FMP age in different countries span about 4 years¹⁸) and another that is wider due to

added noise (orange, $s^2 = s_0^2 + 4^2$) (larger than typical FMP self-report error noise -1 year^{39,46}). **b)** deconvolving with YoGlen method 1 using an FMP distribution that has a shifted mean has negligible effect on YoGlen output. **c)** Deconvolving with YoGlen method 1 using an FMP distribution that is wider due to excess noise has negligible effect on YoGlen output. **d)** and **e)** same for YoGlen method 2.



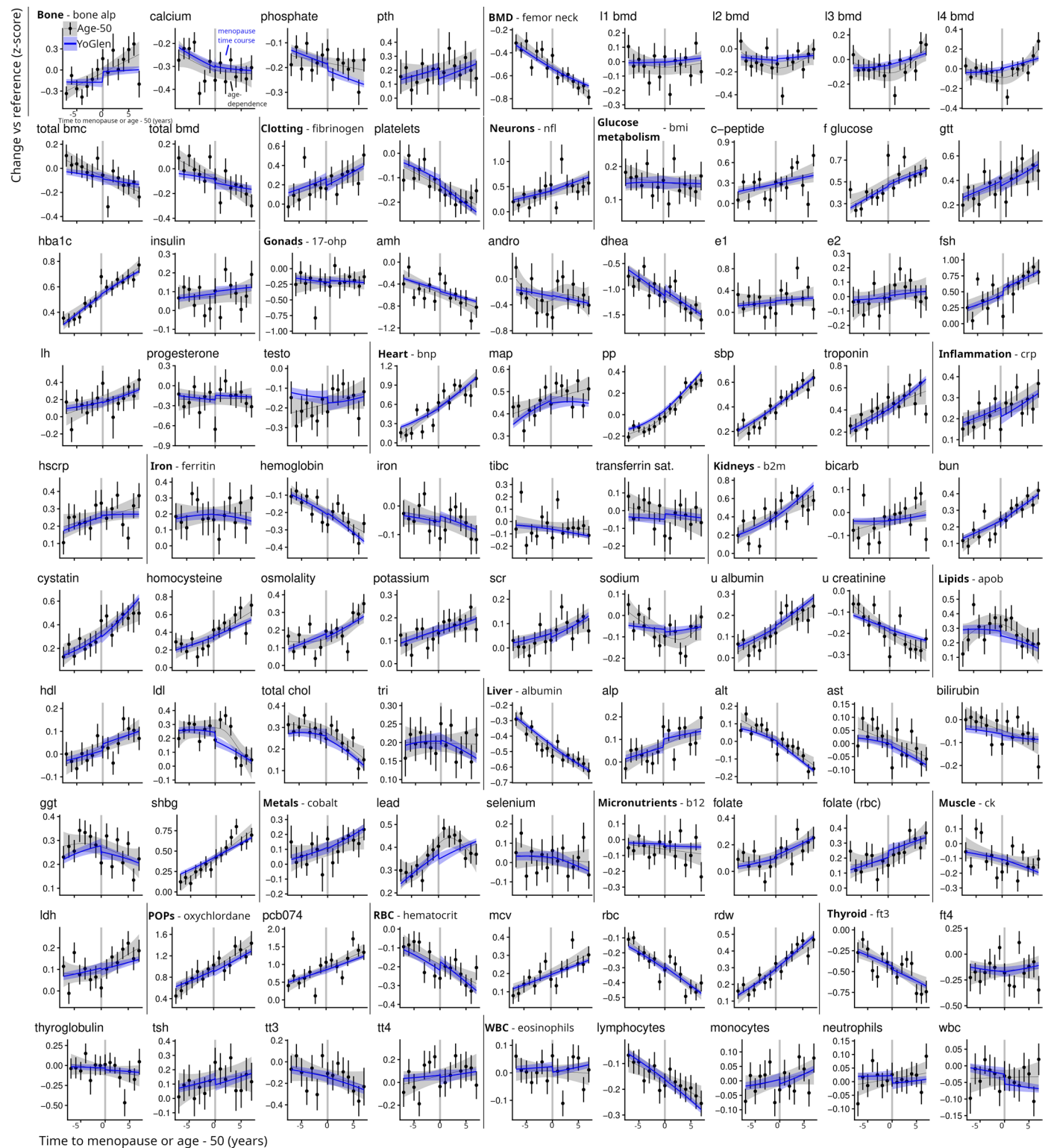
Extended Data Fig. 2 | Validation of YoGlen using simulated data. We used YoGlen model 1 fits from Fig. 2 for 90 tests as a reference to generate simulated data (gray points) by drawing age and FMP age from the NHANES distribution and generating lab test values according to the reference fits (correlations and variances were also matched to NHANES). The simulated population size was equal to the observed population size ($N = 36,356$). We then hid the FMP ages larger than current age, and used YoGlen model 1 to reconstruct the fit as in Fig. 2 (black, correct FMP distribution). The agreement in the unknown region (time to menopause < 0) with the reference fit was excellent, Pearson's $r = 0.97$ ($p < 10^{-15}$, two-sided test). To test sensitivity to errors in the FMP distribution, we repeated

the analysis using altered FMP distributions as in Extended Data Fig. 1a, with mean shifted later by 4 years (green curve), and excess noise (adding a random number to FMP from a normal distribution with mean 0 and s.d. of 4 years, orange curve). YoGlen was insensitive to these changes to FMP distribution, as evidenced by the excellent agreement with the original reference fit, Pearson's $r = 0.94$ (shift FMP) and $r = 0.96$ (noisy FMP) (both $p < 10^{-15}$, two-sided tests). This indicates YoGlen is robust against observational noise and errors in FMP age. The simulation was based on the initial version of the paper and therefore differs slightly from the main text, but the validation is equally valid.



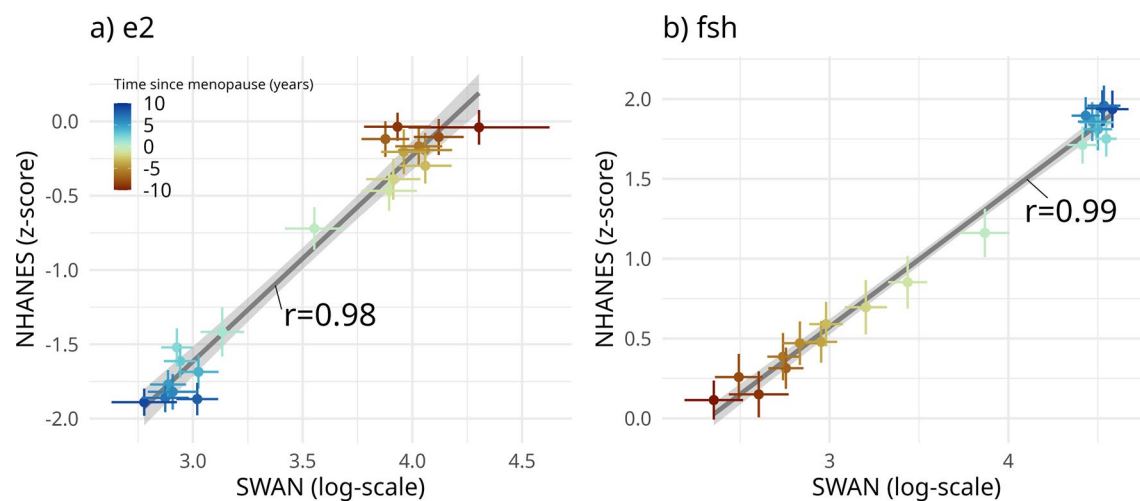
Extended Data Fig. 3 | Female lab tests show jumps at the FMP. zoomed in to -7 to 7 years around the FMP (NHANES). Plotted are the cross-sectional mean test values per year of age versus age minus 50 (gray), and the YoGlen timeto-FMP where $t = 0$ is the FMP (blue). Time=0 on the x axis corresponds to 50 years for the

gray curves, and to the age of FMP for the blue curves. Black line is 10-knot spline fit to age; blue line is 10 fold, 10 repeat cross-validation model average fit to time to menopause, the same as in Fig. 2. NHANES median $n = 14778$, IQR: 5481-29431 people, see Extended Data Table 1.



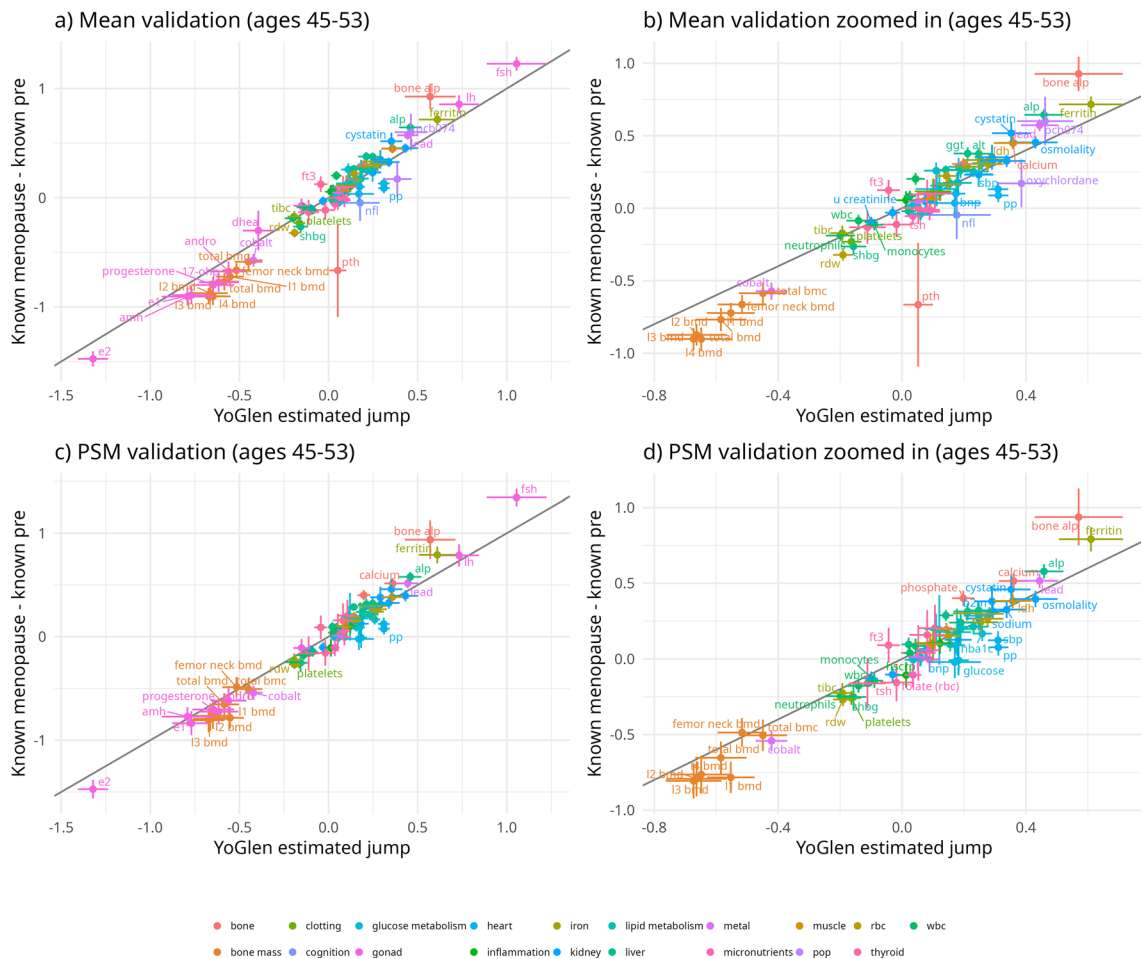
Extended Data Fig. 4 | Male lab tests do not show a jump. when analyzed with the same YoGlen algorithm and FMP distribution as females (NHANES). Plotted are the cross-sectional mean test values per year of age versus age minus 50 (gray), and the YoGlen time-to-FMP (blue). Black line is 10-knot spline fit to

age; blue line is 10 fold, 10 repeat cross-validation model average fit to time to menopause, the same as in Fig. 2. NHANES median n = 13320, IQR: 5883-29914 people, see Extended Data Table 1.



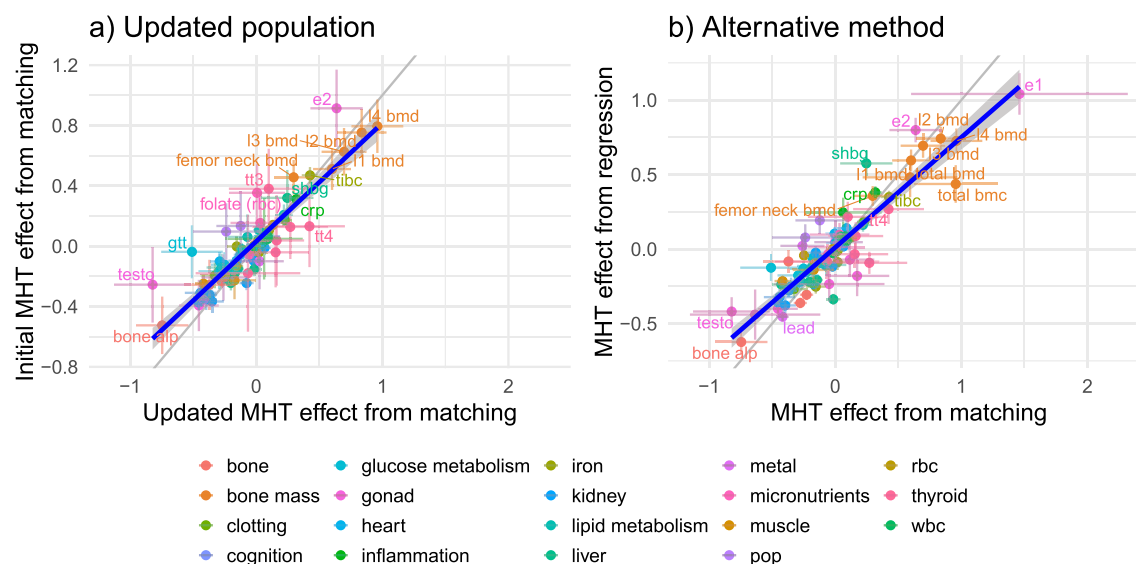
Extended Data Fig. 5 | Validation of YoGlen method (NHANES) by comparison to the longitudinal Study of Women's Health Across the Nation (SWAN) for the key sex hormones. a) e2 (Pearson's $r = 0.98$, $p = 10^{-14}$, two-sided test.) b) fsh ($r = 0.99$, $p < 10^{-15}$, two-sided test). 1-year bins from -10 to 10 years before/after

menopause. SWAN data are logscaled; NHANES data are log-scaled then z-scored by healthy reference (Extended Data Table 1). NHANES: n e2 = 8298, n fsh = 4826; SWAN: n e2 = 872, n fsh = 878.



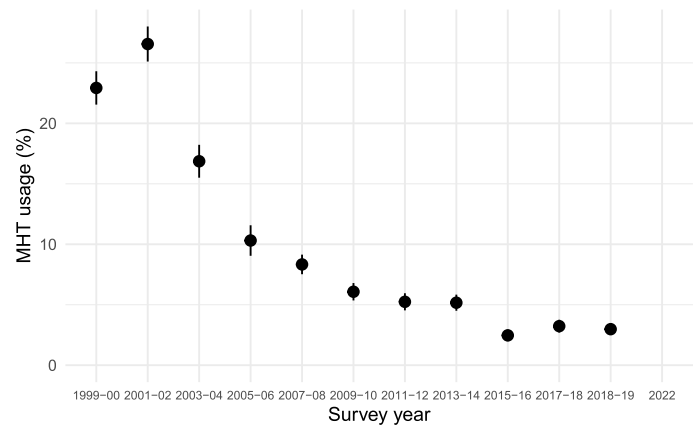
Extended Data Fig. 6 | Sensitivity analysis of jump sizes. shows strong concordance between YoGlen and direct estimates (NHANES). We compared the difference between pre-menopausal and post-menopausal females aged 45–53 who did not have a hysterectomy with known menopause status (y-axis) to the YoGlen estimates from Fig. 2 (x-axis), both with (left) and without (right) the sex hormones. **a)** We see strong concordance between the mean difference and YoGlen estimate, with Pearson's $\rho = 0.97$ (0.95–0.98 95% CI, $p = 10^{-16}$; $n = 3155$ individuals, two-sided test). **b)** Same as figure **a)** but zoomed in (that is, excluding

sex hormones). **c)** We see strong concordance with the mean propensity-score matched (PSM) differences and the YoGlen estimate. Pearson's $\rho = 0.98$ (0.97–0.99 95% CI, $p = 10^{-16}$, $n = 890$ pairs, two-sided test). **d)** Same as figure **c)** but zoomed in. Known menopause status only. PSM is paired difference after matching based on: poverty, smoking, insurance, diabetes, pre vs post 2005, black ethnicity and 'some college' (or more) education level (all balanced, with absolute mean difference and KS threshold of 0.1⁴¹). Minimum 50 measurements per test.



Extended Data Fig. 7 | Sensitivity analysis of menopaual hormone therapy (MHT) effect sizes. indicates that the results are robust to changing the population (**a**) and changing the estimating algorithm (**b**). **a**) Our initial effect sizes estimated using self-reported MHT status from years 1999–2012 only (y-axis) correlated strongly with our updated estimates including specific drugs used for years 1999–2019 (x-axis), $r = 0.90$ (95% CI: 0.85–0.93, $p = 10^{-16}$, two-sided test); propensity-score matched. **b**) Estimates using ordinary linear regression

(y-axis) correlate strongly with our updated estimates $r = 0.90$ (95% CI: 0.86–0.94, $p = 10^{-16}$, two-sided test). Propensity-score matched using: survey period (pre vs post 2005), menopause status, age, poverty income ratio, smoker status, insurance status, diabetes status, black ethnicity (updated only) and education. Ordinary linear regression used: male age-dependence from 10-knot thin-plate spline⁴⁴, survey year, menopause status, age, poverty income ratio, smoker status, insurance status, diabetes status, all ethnicities and education.



Extended Data Fig. 8 | Menopausal hormone therapy (MHT) usage reported in NHANES dropped around 2004, as seen globally in the wake of the Women’s Health Initiative (WHI) study⁴⁷. MHT usage among post-menopausal females.

Includes both self-reported usage (asked until 2013–2014) and generic estradiol drug usage (asked each year except 2022). The overall frequency from 1999–2019 was 9.0% (N = 11443 individuals).

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For all statistical analyses, confirm that the following items are present in the figure legend, table legend, main text, or Methods section.

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| ☐ | ☒ | The exact sample size (n) for each experimental group/condition, given as a discrete number and unit of measurement |
| ☐ | ☒ | A statement on whether measurements were taken from distinct samples or whether the same sample was measured repeatedly |
| ☐ | ☒ | The statistical test(s) used AND whether they are one- or two-sided
<i>Only common tests should be described solely by name; describe more complex techniques in the Methods section.</i> |
| ☐ | ☒ | A description of all covariates tested |
| ☐ | ☒ | A description of any assumptions or corrections, such as tests of normality and adjustment for multiple comparisons |
| ☐ | ☒ | A full description of the statistical parameters including central tendency (e.g. means) or other basic estimates (e.g. regression coefficient) AND variation (e.g. standard deviation) or associated estimates of uncertainty (e.g. confidence intervals) |
| ☐ | ☒ | For null hypothesis testing, the test statistic (e.g. F , t , r) with confidence intervals, effect sizes, degrees of freedom and P value noted
<i>Give P values as exact values whenever suitable.</i> |
| ☒ | ☐ | For Bayesian analysis, information on the choice of priors and Markov chain Monte Carlo settings |
| ☒ | ☐ | For hierarchical and complex designs, identification of the appropriate level for tests and full reporting of outcomes |
| ☐ | ☒ | Estimates of effect sizes (e.g. Cohen's d , Pearson's r), indicating how they were calculated |

Our web collection on [statistics for biologists](#) contains articles on many of the points above.

Software and code

Policy information about [availability of computer code](#)

Data collection No data were collected

Data analysis <https://github.com/AlonLabWIS/yoglen>

For manuscripts utilizing custom algorithms or software that are central to the research but not yet described in published literature, software must be made available to editors and reviewers. We strongly encourage code deposition in a community repository (e.g. GitHub). See the Nature Portfolio [guidelines for submitting code & software](#) for further information.

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All manuscripts must include a [data availability statement](#). This statement should provide the following information, where applicable:

- Accession codes, unique identifiers, or web links for publicly available datasets
- A description of any restrictions on data availability
- For clinical datasets or third party data, please ensure that the statement adheres to our [policy](#)

Aggregated and simulated data are available on GitHub: <https://github.com/AlonLabWIS/YoGlen>. Individualized data for NHANES can be downloaded from <https://www.cdc.gov/nchs/nhanes/>. Individualized data from Clalit are not publicly available. Quantiles for the healthy, no meds Clalit data are available at <https://tanaylab.weizmann.ac.il/labs/>.

Research involving human participants, their data, or biological material

Policy information about studies with [human participants or human data](#). See also policy information about [sex, gender \(identity/presentation\), and sexual orientation](#) and [race, ethnicity and racism](#).

Reporting on sex and gender	All analysis was sex-stratified. The GitHub repository includes aggregate data for each sex.
Reporting on race, ethnicity, or other socially relevant groupings	Black ethnicity was included for propensity score matching as black females had much higher bone mineral density than non-black (U-test $p=1E-16$, mean difference: 0.75 ± 0.02 z-score total BMD).
Population characteristics	Males and females ages 20+ for NHANES and ages 30-70 for Clalit. Pregnant females were excluded.
Recruitment	This is a secondary analysis, we did not recruit specifically for this study. NHANES data are from a publicly available study. Clalit data are all-comers electronic medical records from 2004-2024.
Ethics oversight	Data acquisition was approved by the Clalit Helsinki Committee RMC-1059-20.

Note that full information on the approval of the study protocol must also be provided in the manuscript.

Field-specific reporting

Please select the one below that is the best fit for your research. If you are not sure, read the appropriate sections before making your selection.

☒ Life sciences ☐ Behavioural & social sciences ☐ Ecological, evolutionary & environmental sciences

For a reference copy of the document with all sections, see [nature.com/documents/nr-reporting-summary-flat.pdf](https://www.nature.com/documents/nr-reporting-summary-flat.pdf)

Life sciences study design

All studies must disclose on these points even when the disclosure is negative.

Sample size	This is a secondary analysis, we did not recruit for this study. Clalit includes 1.05 million females (+paired males); NHANES includes 38000 females (+paired males).
Data exclusions	Pregnancies were excluded. Pregnancy is associated with very high estradiol (~10x higher than normal) that could confounder our results.
Replication	We analyzed two separate studies, NHANES and Clalit, and confirmed concordance of our key results (Figure 2c, Figure 3c and Figure 4). We additionally validated our estradiol and follicle stimulating hormone deconvolution trajectories using Study of Women's Health Across the Nation: SWAN as shown in Supplemental Figure S5. We also performed within-study sensitivity analyses in Supplemental Figures S7 and S8.
Randomization	We adjusted for covariates in the HRT analysis using two approaches: propensity score matching and linear regression. Both approaches showed strong concordance on the resulting HRT effect sizes $r=0.90$, $p=1E-16$, Supplementary Fig S8. We included covariates: menopause status, age, poverty income ratio, smoker status, insurance status, diabetes status, ethnicity and education.
Blinding	Clalit and NHANES were separately analyzed by different authors.

Reporting for specific materials, systems and methods

We require information from authors about some types of materials, experimental systems and methods used in many studies. Here, indicate whether each material, system or method listed is relevant to your study. If you are not sure if a list item applies to your research, read the appropriate section before selecting a response.

Materials & experimental systems

n/a	Involved in the study
☐	☐ Antibodies
☐	☐ Eukaryotic cell lines
☐	☐ Palaeontology and archaeology
☐	☐ Animals and other organisms
☐	☐ Clinical data
☐	☐ Dual use research of concern
☐	☐ Plants

Methods

n/a	Involved in the study
☐	☐ ChIP-seq
☐	☐ Flow cytometry
☐	☐ MRI-based neuroimaging

Antibodies

Antibodies used	Describe all antibodies used in the study; as applicable, provide supplier name, catalog number, clone name, and lot number.
Validation	Describe the validation of each primary antibody for the species and application, noting any validation statements on the manufacturer's website, relevant citations, antibody profiles in online databases, or data provided in the manuscript.

Eukaryotic cell lines

Policy information about [cell lines and Sex and Gender in Research](#)

Cell line source(s)	State the source of each cell line used and the sex of all primary cell lines and cells derived from human participants or vertebrate models.
Authentication	Describe the authentication procedures for each cell line used OR declare that none of the cell lines used were authenticated.
Mycoplasma contamination	Confirm that all cell lines tested negative for mycoplasma contamination OR describe the results of the testing for mycoplasma contamination OR declare that the cell lines were not tested for mycoplasma contamination.
Commonly misidentified lines (See ICLAC register)	Name any commonly misidentified cell lines used in the study and provide a rationale for their use.

Palaeontology and Archaeology

Specimen provenance	Provide provenance information for specimens and describe permits that were obtained for the work (including the name of the issuing authority, the date of issue, and any identifying information). Permits should encompass collection and, where applicable, export.
Specimen deposition	Indicate where the specimens have been deposited to permit free access by other researchers.
Dating methods	If new dates are provided, describe how they were obtained (e.g. collection, storage, sample pretreatment and measurement), where they were obtained (i.e. lab name), the calibration program and the protocol for quality assurance OR state that no new dates are provided.
☐ Tick this box to confirm that the raw and calibrated dates are available in the paper or in Supplementary Information.	
Ethics oversight	Identify the organization(s) that approved or provided guidance on the study protocol, OR state that no ethical approval or guidance was required and explain why not.

Note that full information on the approval of the study protocol must also be provided in the manuscript.

Animals and other research organisms

Policy information about [studies involving animals; ARRIVE guidelines](#) recommended for reporting animal research, and [Sex and Gender in Research](#)

Laboratory animals	For laboratory animals, report species, strain and age OR state that the study did not involve laboratory animals.
Wild animals	Provide details on animals observed in or captured in the field; report species and age where possible. Describe how animals were caught and transported and what happened to captive animals after the study (if killed, explain why and describe method; if released, say where and when) OR state that the study did not involve wild animals.
Reporting on sex	Indicate if findings apply to only one sex; describe whether sex was considered in study design, methods used for assigning sex. Provide data disaggregated for sex where this information has been collected in the source data as appropriate; provide overall numbers in this Reporting Summary. Please state if this information has not been collected. Report sex-based analyses where performed, justify reasons for lack of sex-based analysis.
Field-collected samples	For laboratory work with field-collected samples, describe all relevant parameters such as housing, maintenance, temperature, photoperiod and end-of-experiment protocol OR state that the study did not involve samples collected from the field.
Ethics oversight	Identify the organization(s) that approved or provided guidance on the study protocol, OR state that no ethical approval or guidance was required and explain why not.

Note that full information on the approval of the study protocol must also be provided in the manuscript.

Clinical data

Policy information about [clinical studies](#)

All manuscripts should comply with the ICMJE [guidelines for publication of clinical research](#) and a completed [CONSORT checklist](#) must be included with all submissions.

Clinical trial registration	<i>Provide the trial registration number from ClinicalTrials.gov or an equivalent agency.</i>
Study protocol	<i>Note where the full trial protocol can be accessed OR if not available, explain why.</i>
Data collection	<i>Describe the settings and locales of data collection, noting the time periods of recruitment and data collection.</i>
Outcomes	<i>Describe how you pre-defined primary and secondary outcome measures and how you assessed these measures.</i>

Dual use research of concern

Policy information about [dual use research of concern](#)

Hazards

Could the accidental, deliberate or reckless misuse of agents or technologies generated in the work, or the application of information presented in the manuscript, pose a threat to:

No	Yes
☐	☐ Public health
☐	☐ National security
☐	☐ Crops and/or livestock
☐	☐ Ecosystems
☐	☐ Any other significant area

Experiments of concern

Does the work involve any of these experiments of concern:

No	Yes
☐	☐ Demonstrate how to render a vaccine ineffective
☐	☐ Confer resistance to therapeutically useful antibiotics or antiviral agents
☐	☐ Enhance the virulence of a pathogen or render a nonpathogen virulent
☐	☐ Increase transmissibility of a pathogen
☐	☐ Alter the host range of a pathogen
☐	☐ Enable evasion of diagnostic/detection modalities
☐	☐ Enable the weaponization of a biological agent or toxin
☐	☐ Any other potentially harmful combination of experiments and agents

Plants

Seed stocks	<i>Report on the source of all seed stocks or other plant material used. If applicable, state the seed stock centre and catalogue number. If plant specimens were collected from the field, describe the collection location, date and sampling procedures.</i>
Novel plant genotypes	<i>Describe the methods by which all novel plant genotypes were produced. This includes those generated by transgenic approaches, gene editing, chemical/radiation-based mutagenesis and hybridization. For transgenic lines, describe the transformation method, the number of independent lines analyzed and the generation upon which experiments were performed. For gene-edited lines, describe the editor used, the endogenous sequence targeted for editing, the targeting guide RNA sequence (if applicable) and how the editor was applied.</i>
Authentication	<i>Describe any authentication procedures for each seed stock used or novel genotype generated. Describe any experiments used to assess the effect of a mutation and, where applicable, how potential secondary effects (e.g. second site T-DNA insertions, mosaicism, off-target gene editing) were examined.</i>

ChIP-seq

Data deposition

- ☐ Confirm that both raw and final processed data have been deposited in a public database such as [GEO](#).
- ☐ Confirm that you have deposited or provided access to graph files (e.g. BED files) for the called peaks.

Data access links

May remain private before publication.

For "Initial submission" or "Revised version" documents, provide reviewer access links. For your "Final submission" document, provide a link to the deposited data.

Files in database submission

Provide a list of all files available in the database submission.

Genome browser session

(e.g. [UCSC](#))

Provide a link to an anonymized genome browser session for "Initial submission" and "Revised version" documents only, to enable peer review. Write "no longer applicable" for "Final submission" documents.

Methodology

Replicates

Describe the experimental replicates, specifying number, type and replicate agreement.

Sequencing depth

Describe the sequencing depth for each experiment, providing the total number of reads, uniquely mapped reads, length of reads and whether they were paired- or single-end.

Antibodies

Describe the antibodies used for the ChIP-seq experiments; as applicable, provide supplier name, catalog number, clone name, and lot number.

Peak calling parameters

Specify the command line program and parameters used for read mapping and peak calling, including the ChIP, control and index files used.

Data quality

Describe the methods used to ensure data quality in full detail, including how many peaks are at FDR 5% and above 5-fold enrichment.

Software

Describe the software used to collect and analyze the ChIP-seq data. For custom code that has been deposited into a community repository, provide accession details.

Flow Cytometry

Plots

Confirm that:

- ☐ The axis labels state the marker and fluorochrome used (e.g. CD4-FITC).
- ☐ The axis scales are clearly visible. Include numbers along axes only for bottom left plot of group (a 'group' is an analysis of identical markers).
- ☐ All plots are contour plots with outliers or pseudocolor plots.
- ☐ A numerical value for number of cells or percentage (with statistics) is provided.

Methodology

Sample preparation

Describe the sample preparation, detailing the biological source of the cells and any tissue processing steps used.

Instrument

Identify the instrument used for data collection, specifying make and model number.

Software

Describe the software used to collect and analyze the flow cytometry data. For custom code that has been deposited into a community repository, provide accession details.

Cell population abundance

Describe the abundance of the relevant cell populations within post-sort fractions, providing details on the purity of the samples and how it was determined.

Gating strategy

Describe the gating strategy used for all relevant experiments, specifying the preliminary FSC/SSC gates of the starting cell population, indicating where boundaries between "positive" and "negative" staining cell populations are defined.

- ☐ Tick this box to confirm that a figure exemplifying the gating strategy is provided in the Supplementary Information.

Magnetic resonance imaging

Experimental design

Design type

Indicate task or resting state; event-related or block design.

Design specifications

Specify the number of blocks, trials or experimental units per session and/or subject, and specify the length of each trial or block (if trials are blocked) and interval between trials.

Behavioral performance measures

State number and/or type of variables recorded (e.g. correct button press, response time) and what statistics were used to establish that the subjects were performing the task as expected (e.g. mean, range, and/or standard deviation across subjects).

Acquisition

Imaging type(s)

Specify: functional, structural, diffusion, perfusion.

Field strength

Specify in Tesla

Sequence & imaging parameters

Specify the pulse sequence type (gradient echo, spin echo, etc.), imaging type (EPI, spiral, etc.), field of view, matrix size, slice thickness, orientation and TE/TR/flip angle.

Area of acquisition

State whether a whole brain scan was used OR define the area of acquisition, describing how the region was determined.

Diffusion MRI

☐ Used

☐ Not used

Preprocessing

Preprocessing software

Provide detail on software version and revision number and on specific parameters (model/functions, brain extraction, segmentation, smoothing kernel size, etc.).

Normalization

If data were normalized/standardized, describe the approach(es): specify linear or non-linear and define image types used for transformation OR indicate that data were not normalized and explain rationale for lack of normalization.

Normalization template

Describe the template used for normalization/transformation, specifying subject space or group standardized space (e.g. original Talairach, MNI305, ICBM152) OR indicate that the data were not normalized.

Noise and artifact removal

Describe your procedure(s) for artifact and structured noise removal, specifying motion parameters, tissue signals and physiological signals (heart rate, respiration).

Volume censoring

Define your software and/or method and criteria for volume censoring, and state the extent of such censoring.

Statistical modeling & inference

Model type and settings

Specify type (mass univariate, multivariate, RSA, predictive, etc.) and describe essential details of the model at the first and second levels (e.g. fixed, random or mixed effects; drift or auto-correlation).

Effect(s) tested

Define precise effect in terms of the task or stimulus conditions instead of psychological concepts and indicate whether ANOVA or factorial designs were used.

Specify type of analysis: ☐ Whole brain ☐ ROI-based ☐ Both

Statistic type for inference

Specify voxel-wise or cluster-wise and report all relevant parameters for cluster-wise methods.

(See [Eklund et al. 2016](#))

Correction

Describe the type of correction and how it is obtained for multiple comparisons (e.g. FWE, FDR, permutation or Monte Carlo).

Models & analysis

n/a | Involved in the study

☐ ☐ Functional and/or effective connectivity

☐ ☐ Graph analysis

☐ ☐ Multivariate modeling or predictive analysis

Functional and/or effective connectivity

Report the measures of dependence used and the model details (e.g. Pearson correlation, partial correlation, mutual information).

Graph analysis

Report the dependent variable and connectivity measure, specifying weighted graph or binarized graph, subject- or group-level, and the global and/or node summaries used (e.g. clustering coefficient, efficiency, etc.).

Multivariate modeling and predictive analysis

Specify independent variables, features extraction and dimension reduction, model, training and evaluation metrics.