Human hormone seasonality

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Hormones of the pituitary control the major biological functions of stress, growth, metabolism and reproduction. In animals these hormones show pronounced seasonality, with different set points for different seasons. In humans, the seasonality of these hormones has rarely been studied in a large enough dataset to discern common patterns. Here, we analyze an Israeli health record on 46 million person-years, including millions of hormone blood tests. We find clear seasonal patterns: the pituitary hormones peak in summer, whereas their downstream effector hormones are in anti-phase, and peak in winter-spring. This anti-phase is unexpected because the pituitary hormones control the downstream hormones. We show that the antiphase can arise from changes in the mass of the glands due to trophic effects of the hormones, generating a feedback circuit with a natural frequency of about a year that can entrain to the seasons. Thus, humans may show coordinated seasonal set-points with a winter-spring peak in the growth, stress adaptation, metabolism and reproduction axes.

Keywords: hypothalamic-pituitary-adrenal axis, HPA axis, hypothalamic-pituitary-gonadal axis, hypothalamic-pituitary-thyroid axis.

Introduction

The pituitary hormones control major biological functions in mammals, including growth, reproduction, metabolism and stress adaptation. Each of these functions has a dedicated hormonal axis, in which signals from the hypothalamus cause secretion of the pituitary hormone into the bloodstream. The pituitary hormone instructs a peripheral organ to secrete effector hormones with widespread effects on many tissues. For example, stress response is governed by the hypothalamic-pituitary-adrenal (HPA) axis: physiological and psychological stress signals cause the hypothalamus to induce secretion of ACTH from the pituitary, which instructs the adrenal cortex to secrete cortisol. These axes act to maintain physiological setpoints, which can change in different situations, a concept known as allostasis (McEwen, 1998).

A major reason that organisms change their setpoints is the seasons. Animals show seasonal changes in the pituitary and effector hormones that govern seasonality in reproduction, activity, growth, pigmentation, morphology and migration (Gwinner, 2012). Animals even show these changes with a circannual rhythm when maintained in constant photoperiod and temperature conditions (Zucker, 2001; Lincoln et al., 2006;

Gwinner, 2012). The fact that hormones can cycle without external signals suggests an internal oscillator with a period of about one year. The location of this oscillator is unclear, with some evidence of an involvement of melatonin signals to the pars tuberalis of the pituitary (Wood *et al.*, 2015; Wood and Loudon, 2018).

Whether hormones show seasonality in humans has not been studied comprehensively by tracking all hormone in a large number of participants. Each axis has been studied separately, usually with small samples. These studies suggest that thyroid hormones and saliva cortisol show seasonality on the order of 10%. The studies are limited by considerations of circadian rhythms which affects cortisol and several other hormones.

To study human hormone seasonality requires a large dataset with a comprehensive coverage of all hormones. Here we provide such as study using an Israeli medical record database with millions of blood tests. We address the circadian rhythm concern using the time of each test. We find coordinated seasonality with a spring peak in effector hormones and a surprising antiphase between pituitary and effector hormones. We provide an explanation for this antiphase by showing that trophic effects of the hormones create an oscillatory circuit in which the functional mass of the glands changes over the year and can entrain to yearly signals. The results support a winter-spring peak for human reproduction, metabolism, growth and stress adaptation.

Results

Data on millions of blood tests shows seasonality

We analyzed electronic medical record data from a large Israeli medical insurer (Clalit), which includes millions of blood tests (Fig 1). The dataset includes about half of the Israeli population over 15 years (2002-2017) totaling 46 million life-years, with broad socioeconomic and ethnic representation.

Electronic medical records have the challenge of ascertainment bias, because the tests are done for medical reasons. To address this, for each blood test we removed data from pregnant women, individuals with medical conditions that affect the blood test, and individuals that take drugs that affect the blood test (Methods).

We considered male and females separately and binned age groups from 20-80 by decades (data for age range 20-50 is similar, SI). We performed quantile analysis in each decade to avoid age-related trends and outliers. Seasonality was assessed by cosinor tests (SI).

One concern is hormone circadian rhythms, raising the question of the time of day the test was taken relative to the person's circadian cycle. To address this, we obtained the time of day of each test. The seasonality conclusions presented below are unaffected by considering only tests done at specific times of day, or by considering only tests done at a fixed time interval (2.5h) from dawn (SI). We also compared blood tests from one of the most circadian hormones, cortisol, to urine tests that gather cortisol over 24 hours, and find similar seasonality. We conclude that we can effectively control for circadian effects.

The data allowed us to consider all pituitary and effector hormones in a single framework. Hormones secreted by the anterior pituitary for reproduction (LH), metabolism (TSH), and lactation (PRL), showed seasonal oscillations that peak in summer, July or August. The pituitary stress hormone ACTH in females has much fewer tests but also shows a trend to a May-June peak, whereas data for males preclude identifying seasonality. The amplitude is on the order of 1-3 percentiles. This seasonality

can be detected by virtue of the large number of tests. For example, TSH exceeds 6 million blood tests, resulting in error bars smaller than the dots in Fig 1.

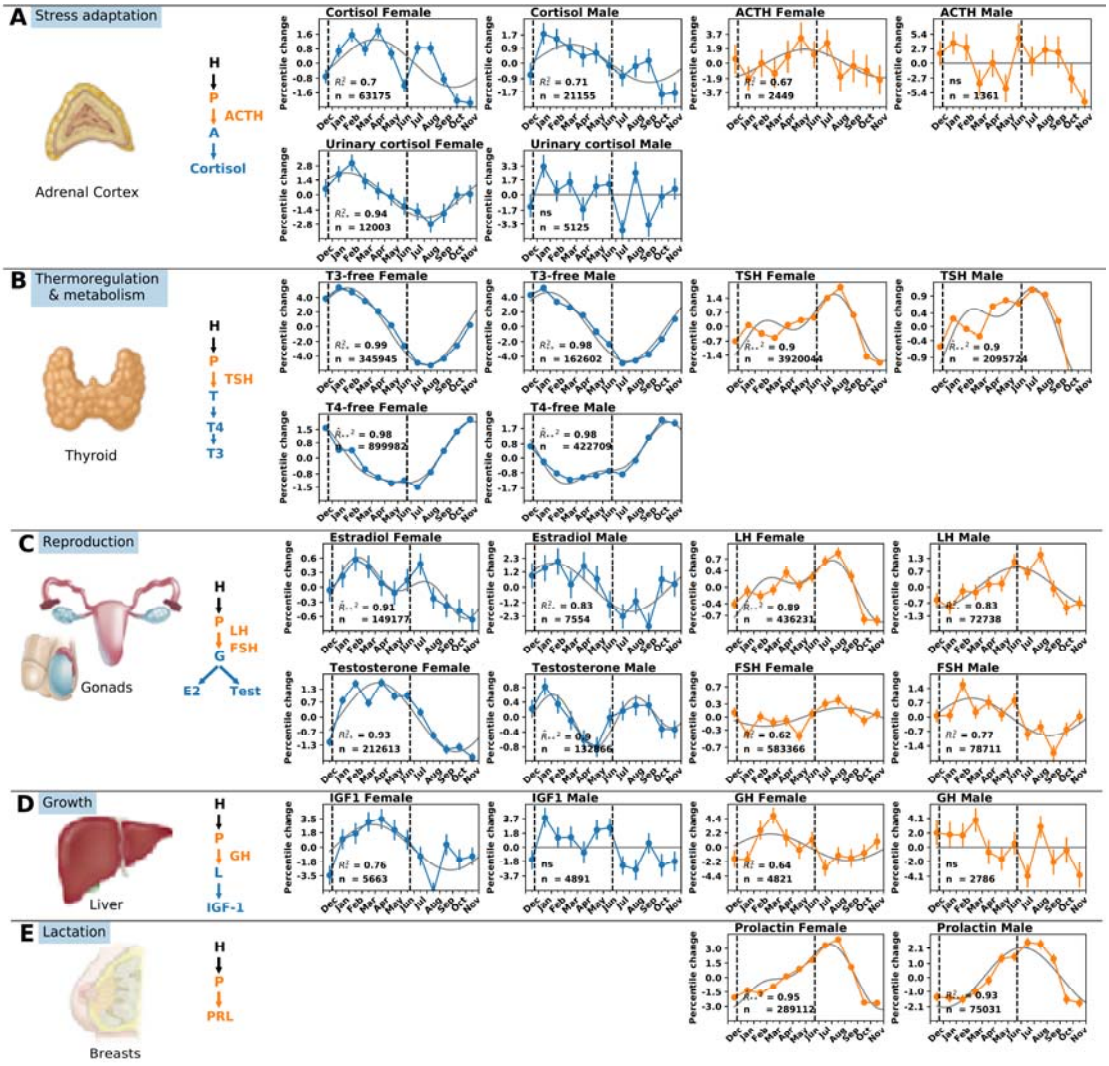


Figure 1. Seasonality of hypothalamic-pituitary axes hormones from Clalit medical records. (A) HPA axis with pituitary hormone ACTH and effector hormone cortisol. (B) Thyroid axis with pituitary hormone TSH (thyroid stimulating hormone) and effector hormones T4, with its derivative T3. (C) Sex axis with pituitary hormones FSH (follicular stimulating hormone) and LH (luteinizing hormone), and effector hormones testosterone and estradiol. (D) Growth axis with pituitary hormone GH (growth hormone) and effector hormone IGF1, (E) lactation pathway with pituitary hormone PRL (prolactin) that controls breast milk production. Each panel indicates the number of tests n, zero-mean cosinor model (gray line) and R^2 where significant (R^2_* - p $< 5 \cdot 10^{-2}$, R^2_{**} - p $< 10^{-3}$, ns - not significant), with first or second order model selected by Aikake criterion (second-order model is indicated by $\wedge$ above R). Vertical dashed lines indicate solstices Dec 21 and Jun21.

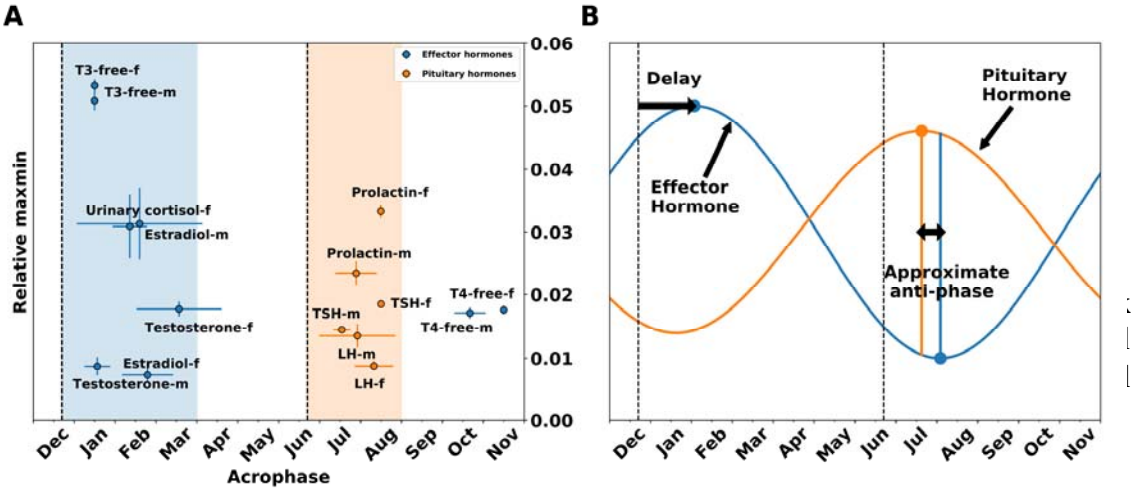
The effector hormones, secreted from peripheral organs under control of the pituitary hormones, also showed seasonality with amplitudes of 1-6 percentiles. In contrast to the summer peak of the pituitary hormones, the effector hormone tests peaked in the winter or spring. The thyroid hormone T3 peaked in winter, in agreement with previous studies (Harrop & Hopton, 1985, Maes *et al.*, 1997), consistent with its role in thermogeneration. Its precursor T4 peaked in late fall. The other effector hormones peaked in late-winter or spring, including the sex hormones testosterone, estradiol, progesterone and the growth hormone IGF1. For cortisol, both blood tests and 24-hour urine tests peaked in February. This late winter peak of cortisol is in agreement with previous studies, including large studies on saliva (Miller *et al.*, 2016) and hair (Abell *et al.*, 2016) cortisol from the UK, as well as smaller studies, including a similar winter peak shifted by 6 months in the southern hemisphere (Hadlow *et al.*, 2014, 2018).

Several hormones showed a secondary peak, forming a biannual rhythm. To analyze this, we used a second-order cosinor model. TSH showed a major peak in august and a minor peak in winter, in agreement with a study on 1.5 million blood tests from Italy (Santi *et al.*, 2009). PRL test showed a similar biannual profile, perhaps due to the upstream regulator TRH that it shares with TSH (Friesen & Hwang, 1975). The tests for the major sex effector hormones estradiol in females and testosterone in males both showed a biannual pattern with a secondary summer peak.

There are two exceptions to the rule that pituitary hormones peak in summer. The tests for pituitary growth hormone, GH, peak in spring, close to its downstream hormone IGF1. We note that like IGF1, GH also acts as an effector hormone, because it regulates growth and metabolism, unlike many other pituitary hormones which mainly have a regulatory role and are not effector hormones. The second exception is FSH in males that peaks in spring.

We also considered blood chemistry tests (ions, glucose, urea). These tests also showed seasonal oscillations with amplitudes on the order of 0.5-8 percentiles (SI). Their peak phases concentrated around Dec21 (shortest photoperiod) June 21 (longest photoperiod, SI). Full data is available in table S1.

We conclude that there is a spring-delay for most of the effector hormone, shifting their peak from Dec 21 to later in the winter or to spring. Additional effector hormones including androgens also show a spring delay (SI). Furthermore, there is a phase shift between most of the effector hormones and their upstream pituitary hormone regulators, placing them in approximate anti-phase (Fig 2B).



Jun21 are indicated (vertical dashed lines), as well as winter-april (blue region) and summer (orange region). m,f indicate male and female. (B) Schematic showing spring shift of effector hormones (blue) and approximate antiphase of the pituitary hormones (orange).

Phase shifts can be due to hormone-driven changes in gland masses

The spring-delay of effector hormones and the approximate antiphase between pituitary and effector hormones are puzzling, given the classical understanding of these axes. The classical model is that each pituitary hormone instructs the release of its effector hormones from peripheral glands and is in turn inhibited by the effector hormones by negative feedback loops (Fig 3A). Delays in these processes are on the order of minutes to days, and are negligible compared to the scale of months required to understand the spring-delay and antiphase. In contrast to the observed blood tests, the classical model predicts that pituitary hormones should coincide with their regulated hormones, and thus have the *same seasonal phase* as the effector hormones that they control (no antiphase). For hormones controlled by photoperiod, the peak should be at the time of extreme photoperiod (eg Dec21), Fig 3A.

To understand the possible mechanism for the spring-delay and antiphase, we considered additional mechanisms that can provide a timescale of months. We focus on the HPA axis because it is well-studied in terms of molecular interactions (Chrousos, 1998); the other axes have analogous interactions (detailed in the SI). We find that a sufficient model for the observed phase shifts arises from adding to the classical model the effect of hormones as the primary growth factors of the tissues that they control (Fig 3B). These interactions are well characterized, but have not been considered on the systems level. In the HPA axis, ACTH not only causes the adrenal to secrete cortisol, it also increases the growth of the adrenal cells (Kataoka, Ikehara and Hattori, 1996; Bicknell *et al.*, 2001). Likewise, CRH not only causes corticotrophs in the pituitary to secrete ACTH, it also increases their growth rate (Westlund et al., 1985; Gertz et al., 1987; Nolan et al., 1998). Thus, the total functional mass of the corticotrophs and adrenal cortex cells are time-dependent variables. They change on the time-scale of weeks, as shown by experiments in rodents (Nolan, Thomas and Levy, 2004), due to both hyperplasia and hypertrophy. The masses of the adrenal and pituitary are also known to change in humans, growing under prolonged stress or major depression and shrinking back when the stress or depression is relieved (Parker, Schatzberg and Lyons, 2003). A similar idea, that seasonal clocks could arise from generation of tissue mass, was named by Lincoln et al the ‘cyclic histogenic hypothesis’ (Hazlerigg & Lincoln, 2011)

We modeled the functional masses together with the classic hormone circuit (eq 1-5 in methods) (Karin *et al.*, 2020). On the timescale of weeks, the HPA axis acts as an oscillator in which the corticotroph and adrenal masses form a negative feedback loop (Fig 3C), with a typical timescale of a year (methods), that can entrain with seasonal input signals.

Simulations and analytical solutions (SI) show that the model entrains to a yearly seasonal input proportional to photoperiod, maximal in Dec 21, and minimal in Jun 21, providing seasonal oscillations to the hormones. The model provides the spring delay and the approximate antiphase: the effector hormone cortisol peaks in spring and the pituitary

hormone ACTH peaks in late summer. The spring shift of cortisol and the antiphase between the hormones is caused by the time it takes the functional cell masses to grow and shrink.

The spring delay and antiphase are found for a wide range of model parameters: the only parameters that affect the phases are the turnover times of the cell functional masses, which can range from a week to a few months and still provide the observed antiphase to within experimental error (SI). All other parameters such as hormone secretion rates and half-lives affect only the dynamics on the scale of hours, and do not measurably affect the seasonal phases.

Similar interactions exist in the other pituitary axes (Plant, 2015; Ortiga-Carvalho *et al.*, 2016). Gland masses also dynamically change in these axes under control of the hormones. For example, thyroid proliferation is activated by the upstream hormone TSH, and thyroid volume changes in humans as exemplified by goiter (Dumont et al., 1992). We provide models for each axis in the SI, finding that they are sufficient to explain the phases in each axis. The models can also explain why GH peaks in spring unlike the other pituitary hormones, due to the very slow turnover time of the peripheral gland in this axis, the liver. The models can also explain the fall peak of the thyroid hormone T4, based on the architecture of cell control in the thyroid axis. Alternative putative mechanisms with slow timescale, such as epigenetic mechanisms or seasonal parameter changes, are also considered in the SI.

Seasonality increases with latitude

The model predicts that the amplitude of seasonal variations should increase with latitude, due to greater photoperiod variation with the seasons. To test this we compared the model with studies from the UK (51^{o}N), Australia (30^{o}S) and Sweden (58^{o}N) on cortisol. The amplitude of cortisol seasonality rose with absolute latitude in agreement with the model predictions (SI) (Fig 3F).

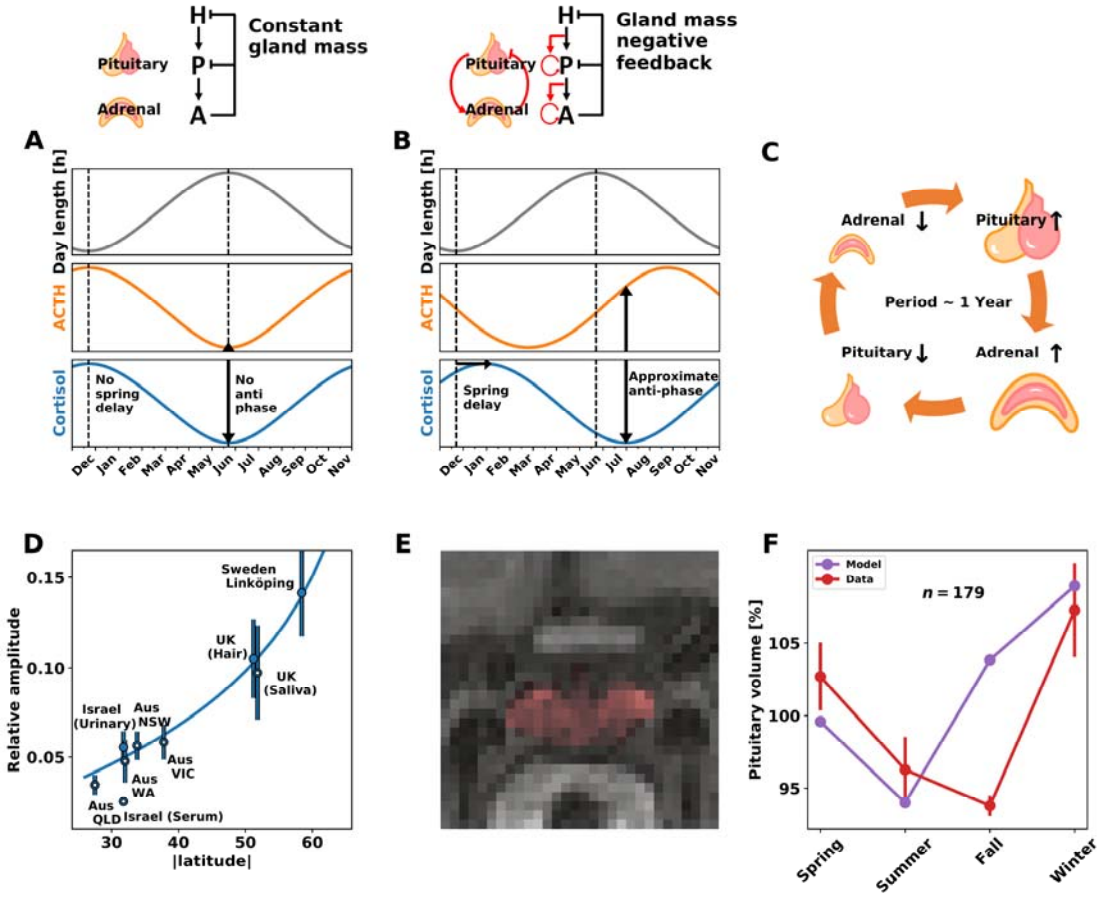


Figure 3. Mechanism for hormone seasonal phases based on a gland-mass oscillator. (A) Classic model of the HPA axis assumes that the mass of the cells that secrete ACTH and cortisol is constant. It predicts that an input maximal in Dec 21 will show both ACTH and cortisol peaks at Dec 21. (B) Model in which consider effect of hormones as growth factors of their downstream glands (red interactions). It predicts a spring delay of cortisol and a summer peak of ACTH. (C) The gland mass model effectively generates a feedback loop in which gland masses can entrain to yearly input cycles. (D) Amplitude of cortisol seasonal variation increases with absolute latitude. Gland-mass model prediction- blue line. Blood tests Australia (Hadlow *et al.* 2018) (open circle), blood (open circle) and urine (circle) tests from present study, saliva (Miler *et al.*, 2016) (open circle) and hair (Abbel *et al.*, 2016) (circle) from UK, and saliva (circle) from Sweden (Persson et al., 2008). (E) Example of pituitary segmented in an MRI image from the UK Biobank. (F) Mean pituitary volume form MRI images binned by four seasons (red). Gland-mass model prediction (purple).

Pituitary volume shows seasonality

The functional mass model makes another testable prediction: the masses of the glands that secrete the hormones should vary with the seasons with specific phases. The total pituitary mass is made of several cell types, including somatotorphs that secrete GH,

thyrotropes that secrete TSH, corticotrophs that secrete ACTH, gonadotrophs that secrete LH/FSH and lactotrophes that secrete PRL, as well as other factors including vasculature. Since we find that the pituitary hormones have similar phases (Fig 1), we reasoned that one can consider total pituitary mass as a single variable. The model then predicts that the pituitary mass should peak in late spring, and thus be (perhaps surprisingly) out pf phase with the levels of the pituitary hormones that peak in late summer. This antiphase is due to the inhibition by the effector hormones – a prediction that is robust to model parameters. To test this, we analyzed a dataset of MRI brain scans and computed the volume of the pituitary. The model shows the same trend but misses by a season. (Fig 3E).

Discussion

We find that human hormone tests show a seasonal pattern with amplitudes on the order of a few percent. Most pituitary hormones peak in late summer, and effector hormones from downstream peripheral organs peak in winter/spring.

The coordinated effector hormone peak suggests that winter/spring is a time of high set-point for reproduction, metabolism, stress adaptation, and growth in humans. This relates favorably to observations on a winter-spring peak of human growth rate (Gelander, Karlberg & Albertsson, 1994; Land et al., 2005; Dalskov et al., 2016), and sperm quality (De Giorgi et al., 2015; Levitas 2013). Human fecundity also peaks in winter-spring in Israel and other countries in temperate clines (Roenneberg and Aschof, 1990), and shifts to later in the year at higher latitudes. The relationship between hormone blood tests and fecundity is complex and affected by cultural factors. Nevertheless, the accumulated data suggests a winter/spring peak not only in effector hormones but also in the biological functions that they control.

The phases observed here, with spring delay in effector hormones and summer peaks of pituitary hormones, are not accounted for by classic descriptions of the hormonal axes. These phases can be explained by the action of the hormones as growth factors for their downstream glands. The gland masses change with the seasons, providing an inertia or memory that can entrain with the seasons. Such an internal 'gland-mass' oscillator may have advantages by keeping track of the seasons, so that a cloudy day in summer is not interpreted as winter. Further tests of this model can measure gland volumes with seasons, and more specifically the total functional masses of the specific hormone-secreting cell types.

This study used large-scale electronic medical records to obtain statistical power that allows a comprehensive view of hormone seasonality at the level of a few percent. To achieve this required filters to address ascertainment bias, including internal controls to remove records from people with illness or medications that affect each hormone, and to address circadian effects. Agreement with smaller-scale seasonality studies on cohorts of healthy individuals, where available, strengthens the confidence in this approach.

This study raises the possibility of an internal seasonal clock in humans that provides a high endocrine set-point for reproduction, growth, metabolism and stress adaptation in winter-spring. It suggests that large-scale medical records can be used to test detailed mechanistic endocrine models and to provide a testing ground for dynamical physiological adaptations in humans.

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Author contributions

Conceptualization, Av.T., A.B., N.M.C, O.K., Y.K., L.M., T.M., M.R., A.M., Am.T. and U.A.; Software, Av.T., A.B., N.M.C., Am.T., and U.A.; Methodology, Av.T. and U.A.; Formal Analysis, Av.T., A.B., N.M.C., Am.T., and U.A.; Investigation, Av.T., A.B., N.M.C., Am.T., and U.A.; Writing – Original Draft, Av.T. and U.A.; Writing – Review & Editing, Av.T., A.B., N.M.C, O.K., Y.K., L.M., T.M., M.R., A.M., Am.T. Supervision, U.A.; Funding Acquisition Am.T. and U.A.

Declaration of Interests

The authors declare no competing interests.

Methods

Equations for the HPA model

The classic HPA hormone cascade with the feedback by cortisol on upstream hormones (Ottesen *et al.*, 2011) can described by:

$$(1)\ \frac{dx_1}{dt} = b_1 u \cdot MR(x_3) \cdot GR(x_3) - a_1 x_1$$

$$(2)\ \frac{dx_2}{dt} = b_2 P x_1 \cdot GR(x_3) - a_2 x_2$$

$$(3)\ \frac{dx_3}{dt} = b_3 A x_2 - a_3 x_3$$

$$(4)\ MR(x_3) = \frac{1}{{x_3}^{n_1}}$$

$$(5)\ GR(x_3) = \frac{1}{1+\left(\frac{x_3}{K_{GR}}\right)^{n_2}}$$

Where the concretion of CRH is x_1, ACTH is x_2 and cortisol is x_3. u is the stress input to the hypothalamus (combined effect of psychological, circadian, seasonal and physiological stresses), b_i are the secretion rates, a_i the hormone removal rates, P and A are the 'gland masses' namely the functional mass of ACTH-secreting pituitary corticotrophs and cortisol-secreting adrenal cortex cells respectively. The equations model the negative feedback in which cortisol provides negative feedback on CRH secretion through MR, and negative feedback on both CRH and ACTH secretion through GR. Equation [4] describes the approximation that MR is at saturation ($[CORT] \gg K_{MR}$), as is commonly assumed under physiological conditions (Andersen,Vinther & Ottesen, 2013; De Kloet *et al.* 1998).

In this study we use the approach of Karin et al (Karin et al., 2020) that adds two new equations to describe the effect of the hormones on the gland sizes. CRH activates P proliferation, and ACTH activates A proliferation:

$$(6)\ \frac{dP}{dt} = P(b_P x_1 - a_P)$$

$$(7)\ \frac{dA}{dt} = A(b_A x_2 - a_A)$$

a_P, a_A are the cell removal rates, and b_P, b_A are the hormone-dependent growth rates. Equations for the timescale of months can be derived by a quasi-steady-state approximation for the hormones, showing a negative feedback loop between P and A

$$(8)\ \frac{dP}{dt} = P\left(c_P u^{\frac{1}{2}} P^{-\frac{1}{2}} A^{-\frac{1}{2}} - a_P\right)$$

$$(9)\ \frac{dA}{dt} = A(c_A u^{\frac{1}{2}} P^{\frac{1}{2}} A^{-\frac{1}{2}} - a_A)$$

Where c_P and c_A are combinations of the parameters (SI).

Modelling

Input to most axes is assumed to be dependent on photoperiod [Wehr, Thomas A., et al. "Conservation of photoperiod-responsive mechanisms in humans." *American Journal of Physiology-Regulatory, Integrative and Comparative Physiology* 265.4 (1993): R846-R857.] Photoperiod dependence on latitude was computed by the astronomical sunrise equation (SI). The relative change in input to the model was proportional to the relative change in day length. If photoperiod varies by W over the year (eg day-length variation of 6-18 hours corresponds to W=0.5), we used $u(t) = 1 + \mathrm{g}\,\mathrm{W}\cos(\omega t)$, where $\omega = \frac{2\pi}{year}$, with maximal input at December 21. We used $g=0.6$, which best fits the latitude dependence of cortisol measurements in Fig 3F. Note that the value of g affects the amplitude but does not measurably affect the phases of the hormone dynamics (SI). We simulated 4 years of seasonal input to avoid transients. In order to simulate the response to a varying day-length input, we simulated the fast equations (Eqs. 1-3) to obtain the numeric quasi-steady-state solution $x_{1,qst}, x_{2,qst}, x_{3,qst}$ for a given input u, P, A. Next, we used these quasi steady-state solutions in Eq 6,7 to find the seasonally varying values of A and P. To simulate morning cortisol blood tests, we computed the steady-state fast equation response to an input u=1, using the seasonally varying value of A and P. Simulations were done using Python.

Electronic Medical record data

The Clalit dataset contains the electronic health records (EHR) of 3.45 million individuals per year on average (Balicer and Afek, 2017). All data was anonymized by hashing of personal identifiers and addresses and randomization of dates by a random number of weeks uniformly sampled between 0 and 13 week for each patient and adding it to all dates in the patient diagnoses, laboratory and medication records. This approach maintained differential data analysis per patient. Diagnoses codes were acquired from both primary care and hospitalization records, and were mapped to the ICD9 coding system. Research was conducted under Clalit Helsinki Committee 0195-17-COM2.

Data processing

Clalit laboratory test records were studied in the age range of 20-50, with men and women analyzed separately. For tests with fewer than 10,000 records (ACTH, urinary

cortisol male, estradiol male, IGF1, GH) we used age range of 20-80 to increase statistical power. For each test we analyzed data from all individuals with no chronic disease with onset 6 months before the test, and no drug that affects the test bought in the 6 months before the test. Chronic disease was defined by non-pediatric ICD9 codes with a Kaplan-Meyer survival drop >10% over 5 years, and which are assigned above a minimal average rate of 1/3 per year. Drugs that affect a test were defined as drugs with significant effect on the test (FDR 0.01). Data was binned by months, correcting for date randomization by subtracting 6.5 weeks. The top and bottom 5% were removed from each month bin. For each test, we then analyzed by quantiles per age decade bin for each gender. Seasonality was identified for each test by bootstrapping the data (with mean subtracted) and comparing to a zero-mean cosinor model $Acos(\omega t + \phi)$ with $\omega = 2\pi/year$ against a null model of a constant level equal to zero. We also tested a second-order cosinor model $Acos(\omega t + \phi) + A' \cos(2\,\omega t + \phi')$ for biannual effects, and selected the best model according to the Akaike information criterion. No tests justified a third-order or higher cosinor model (SI). For each test, phase and amplitude were computed by bootstrapping the error bar of each month (See SI).

Measurement of pituitary volume

Pituitary volumes were measured from MRI images from the Public Human Connectome Project (Glasser *et al.*, 2013; Van Essen *et al.*, 2013). We used 184 T1-weighted high-resolution 3T MR scans from the dataset "WU-Minn HCP". Only this subset contained the image acquisition date and was useful for our seasonal analysis. To segment the pituitary we defined a region of interest (ROI) of 24x24x12 voxels at a fixed coordinates in all scans. The ROI was large enough to contain the pituitary and the hypothalamus in every subject. Manual pituitary segmentations used custom MATLAB software. Repeated segmentation of the same scan agreed well (intersection over union (IoU) mean = 0.895, std = 0.04). 5 scans were excluded from the analysis due to abnormal appearance. Volume of the pituitary (in cm^3) was calculated by summing the areas of the voxels classified as pituitary tissue in the slices and multiplying by a factor of 1.6mm (slice thickness). Finally, pituitary volume was adjusted to represent its proportional volume to the intra-cranial volume (ICV). ICV values for each subject were obtained from the FreeSurfer (Fischl, 2012) datasheet that supplied with the dataset. The manual pituitary segmentation was used to train an automated segmentation algorithm, based on the U-Net deep learning algorithm, a specialized convolutional neural network (CNN) architecture for biomedical image segmentation. Using a training set of 45 scans, the automated algorithm showed good agreement with manual segmentations on the remaining scans.

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