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Title:

Assessment of Menstrual Health Status and Evolution through Mobile Apps for Fertility Awareness

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Abstract

For most women of reproductive age, assessing menstrual health and fertility usually involves regular visits to a gynecologist or another clinician. While these exams provide critical information on an individual's reproductive health status, they typically rely on personal memory, and the results are rarely, if ever, assessed at the population level. In recent years, mobile apps for menstrual tracking have become very popular, allowing us to evaluate the accuracy, reliability and tracking frequency of millions of self-observations, thereby providing an unparalleled view, both in detail and scale, on menstrual health and its evolution. We acquired self-observation data from two mobile apps dedicated to the application of the sympto-thermal fertility awareness method, resulting in a dataset of more than 30 million days of observations from over 2.7 million cycles, where up to 40% of the cycles in which users were seeking pregnancy had recordings every single day. We used a statistical and modeling approach to describe the collected data and investigate ovulation timing. We found that only 24% of ovulations occur at days 14 to 15, that ~20% of luteal phases last for only 10 days or shorter, and that pre-menstrual light bleeding is associated with earlier temperature drop in the late luteal phase. The digital epidemiology approach presented here can help to lead to a better understanding of menstrual health and its connection to women's health overall, which has historically been severely understudied.

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Significance statement

Over 200 million women track their menstrual cycles using mobile phone apps, but it is unclear if these digitally reported data can inform on menstrual health or fertility at the population level. Here we acquired and presented self-observation data of over 2.7 million cycles from two fertility awareness apps. We used a statistical and modeling approach to evaluate the accuracy, reliability and tracking frequency of millions of self-observations. As up to 40% of the cycles in which users were seeking pregnancy had recordings every single day, mobile self-tracking provides a high resolution and long-term view on individual women's patterns, with a strong potential for improved clinical decision making.

Keywords:

Menstrual cycle; mobile phone apps; fertility awareness; digital epidemiology

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Main Text:

A broad diversity of fertility awareness methods (FAMs) has been developed in the past century (1, 2), primarily designed to help couples manage fertility and family planning. Modern methods developed in the last quarter of the 20th century take advantage of the precise description of menstrual variation of the basal body temperature (BBT) or waking temperature, cervical mucus quality and quantity, vaginal sensation, and cervical position (3–6). These methods have defined a set of rules that allows the identification of the fertile window around ovulation, so that couples can adapt their sexual behavior according to their reproductive objectives (7–9). The sympto-thermal method, which combines BBT and cervical mucus observations, is arguably amongst the most reliable FAM for family planning (1, 2, 4, 10). Recently, a number of mobile apps have been developed by private organizations to facilitate FAM tracking. Some of these apps provide their users with automatized interpretation with regard to the opening and closing of the fertility window (11). Over the past few years, an increasing number of women, estimated at over 200 million (12), have started using these apps, contributing to the accumulation of menstrual-related data from a diverse population of users at different stage of life (Fig. 1A).

We were interested in evaluating the potential of the collected data for the assessment of menstrual health, both at the individual level and at the population level, and to help enable better clinical-decision-making processes. We obtained two representative datasets from the apps Kindara (K) and Sympto (S) (11) (Fig. S1A,B, Table S1). Both apps offer similar FAM tracking options but differ in their design and user experience (Fig. S1AB, Table S2). Some of the key differences are (i) the automatic- (S) *vs* user- (K) interpretation of observations, (ii) the per-cycle (S) *vs* per-user (K) definition of fertility goals users wish to achieve, (iii) the criteria for the onset of a new cycle, i.e. fresh bleeding after ovulation (S) *vs* self-assessed or automatic (K), and (iv) the precision at which users can report their observations (SI).

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We investigated the differences in typical use and tracking behavior of regular FAM users during their usual cycles, which we refer to as "*standard cycles*" (Methods). For an idealized ~28-day cycle, FAM-relevant body signs need to be recorded for 8-12 days of each cycle, *i.e.* a tracking frequency of ~ 43%. We found, however, that most regular users report their observations for over 16 days per cycle. For cycles in which users choose to record sexual intercourse (65% (S) – 75% (K) of *standard cycles*), tracking frequency is increased, with over 40% of cycles being tracked every single day when seeking pregnancy (Fig. 1B, S1D), sometimes for long intervals (Fig. 1C).

Confident that users regularly logged observations (Fig. 1B) during *standard cycles*, we sought to characterize general patterns in the observations and frequency of the different FAM body signs. As cycle durations vary by several days, as illustrated in Fig. 2A, and given that the duration of the luteal phase (after ovulation) has been shown to vary less than the follicular phase (before ovulation) (13, 14), we chose to show the ovulation-related observations (BBT, mucus, cervix, vaginal sensation) from the end of each cycle (Fig. 2B-D, S2). Consistently with previous observations on a cohort of much smaller size (15), we observed a clear shift of about 0.36°C/0.7°F in BBT between the mid-follicular phase and the mid-luteal phase (Fig 2B, S2A). BBT showed a decrease at the end of the cycle, as light bleeding or spotting was reported (Fig. 2BC).

In an ovulatory cycle, it is well established that cervical mucus is produced in higher quantity and with a higher stretchiness in the days leading up to ovulation (5, 6, 9, 16), which seems to be observed by users tracking their cervical mucus (85-90% (S) and 40-45% (K) of cycles) (Fig. 2D).

Previous studies have shown that the combination of BBT and cervical mucus variations

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were reliable, although not perfect, proxies for the detection of ovulation (8, 16–18). We therefore decided to define a mathematical framework (HMM) to derive an estimate of the most likely day of ovulation with reliability indicators to reflect the uncertainty of conflicting or unexpected observation patterns (Fig. 3A, S3-5, Methods).

Based on these estimations, we could compare the distribution of cycle length to those of estimated day of ovulation and of luteal phase duration (Fig. 3B) for *cycles with reliable ovulation estimation* (109,161 cycles, Methods). We observed an asymmetrical distribution of cycle length around the typical 27 to 28 days, with a heavy tail on longer cycles. We found a similar asymmetrical distribution for follicular phase duration (or ovulation day), with a median value of 16 days, and 90% of ovulations occurring between day 10 and day 24. Only ~24% of ovulations occurred on days 14 to 15 of the cycle.

Luteal phase duration also displayed an asymmetrical distribution, but with a skew for smaller values and presenting a smaller standard deviation (Fig. 2BC, S4B). Median values were 12 (K) and 13 (S) days, which is in line with a previous study that used fertility monitors (19) but shorter than values reported in studies that used LH peak for timing of ovulation (14, 20). About 35% of cycles have a luteal phase duration of 12 to 13 days, while ~20% of cycles had a luteal phase duration smaller than or equal to 10 days, which represents a higher proportion than reported in a previous epidemiological study (14). We also observed differences between the distributions obtained from the two different apps. These differences might be due to biases found in the user population, especially for users seeking pregnancy that could be at higher risk of sub-fertility if we assume they start tracking after they have already tried to get pregnant for several months (Fig S4C).

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Intrigued by the temporal profile of BBT in the late luteal phase (Fig. 2B), and because we observed many cases in which early temperature drops were concomitant with pre-menstrual bleeding such as illustrated in Fig. 4A, we further investigated the variations in the timing of the end-of-cycle temperature drop and of pre-menstrual bleeding. We defined 4 categories of cycles based on the intensity of pre-menstrual bleeding, including a "no bleeding reported" category. We found that the greater the pre-menstrual bleeding, the earlier the temperature drop and the lower the temperature in the mid/late-luteal phase (Fig. 4B, significantly different BBT distributions, t-test, $p < 0.05$). These observations are consistent with the findings that BBT is positively regulated by progesterone and negatively by estrogen (21). Decreasing BBT would thus reflect decreasing progesterone levels, which is critical for the timing of endometrial shedding (i.e., the menses). These observations could also provide information on how users should report the first day of their period and if light bleeding or spotting should be considered as part of their period, therefore shortening the luteal phase by another 1 or 2 days.

This study's goal was to explore the suitability of datasets collected through two mobile applications (Kindara and Sympto) for the assessment of menstrual health in general, both at the individual level and at the population level. The most obvious potential limitation of this study comes from the origin of the data: a self-selected possibly biased population, limited medical and general information on users, irregular observation patterns and little control on assessing the validity of the observations, in particular with regard to cervical mucus tracking. While the tracking frequency limitation can be alleviated through strict selection of users and cycles (Methods), all other limiting factors might have introduced biases in the present analysis. Prospective studies on selected cohorts with appropriate follow-up and information provided to users will provide higher quality data, which could then be used for comparison.

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Based on the current findings, we suggest that self-tracking of FAM-related body signs provides an affordable means to evaluate the status and evolution of menstrual health. These long term and yet very precise recordings support the idea that the menstrual cycle, like other biological rhythms, is a vital sign whose variations inform about overall health status (22, 23). The digital epidemiology approach (24), where patients collect data themselves through digital means, can in this context represent a powerful method to investigate menstrual health and its connection to women's health at the population level (25) in a field that has historically been severely understudied (26). We believe that users of such applications probably already have an increased awareness of their cycles, and this study shows that these digitally self-tracked observations present an unprecedented opportunity to facilitate the dialog between patients and their clinicians, helping them to make informed decisions based on quantified indicators. The current and future development of evidence-based digital tools for menstrual health monitoring could positively impact women's health, particularly in areas where access to healthcare is limited.

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Methods

Extended Materials and Methods can be found in the Supplementary Information (SI).

Data acquisition

We obtained two de-identified datasets from the Symptotherm foundation (www.sympto.org) and Kindara (www.kindara.com) upon receiving ethical approval from the Canton Geneva ethical commission (CCER Genève, Switzerland), study number 2017-02108. Kindara provided a representative sample of their overall pool of users with at least 4 logged cycles while Sympto provided observations from their long-term users and users who provided their weight, height and menarche age.

Selection criteria for users and cycles

Standard cycles (Sympto: 39,896 cycles; Kindara: 719,182 cycles) denote usual cycles of regular users of the apps. Criteria summary:

- (S&K) not the first cycle of a user nor an on-going cycle
- (S&K) observation gaps were no longer than 15 days within a given cycle
- (S&K) at least one FAM body sign (BBT or cervical mucus or cervix position) was recorded
- (S&K) no mid-cycle period-like bleeding was detected when the cycle was longer than 40 days
- (S) defined as ovulatory cycles by the STM algorithm of Sympto, *i.e.* in which the fertile window could be closed.
- (K) at least 8 FAM observations were reported
- (S) no breastfeeding was reported or peri-menopause was declared
- (K) cycle length was at least 4 days longer than the total number of days in which bleeding was reported

Cycles with reliable ovulation estimation (Sympto: 28,453 cycles; Kindara: 80,708)

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Criteria summary:

- *standard cycles*

- detected temperature shift was at least 0.15C (S) or 0.27F (K) (SI).

- the uncertainty on the ovulation estimation was lower than ±1.5 day (SI).

- the confidence score, which is related to acceptable amount of missing data in the ovulatory period, was equal or higher than 75% (SI).

Observations decoding and ovulation timing estimation with HMM

The FAM body-signs are considered to reflect the hormonal changes orchestrating the menstrual cycles. We were interested in understanding which cycles were reported with observations that were consistent with previous literature description and for which it was thus possible to estimate timing of ovulation. Hidden Markov Models (HMM) are one of the most suitable mathematical frameworks due to its ability to uncover, from observations, latent phenomenon, which are here the cascade of hormonal events across the menstrual cycle. Briefly, we defined a 10-states HMM, in which each state is a particular phase of the menstrual cycle (Fig. 3A top, S3A, SI), and used decoding algorithms (Viterbi – Backward-Forward) to estimate the ovulation time, the uncertainty on this estimation, and a confidence score that accounts for missing observation and variation in temperature taking times.

We then established a set of stringent criteria on the uncertainty of the ovulation estimation (≤ ±1.5 days), the magnitude of the temperature shift (≥ 0.15 C) and the confidence score of the observations (≥ 0.75) to discriminate between cycles for which the estimations could be trusted (*cycles with reliable ovulation estimation*) and those where the observations did not allow for a reliable estimation of the ovulation day (Fig S4A, SI). These strict criteria lead to the exclusion

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of ~40% (Sympto) and ~ 89% (Kindara) of the *standard cycles* that were initially selected. In total, 28,453 (Sympto) + 80,708 (Kindara) *cycles with reliable ovulation estimation* have been used for the subsequent analyses (SI).

Model description

The Hidden Markov Model (HMM) we defined describes a discretization in 10 states of the successive hormonal events throughout an ovulatory menstrual cycle. The HMM definition also includes the probabilities of observing the different FAM reported body signs in each state (emission probabilities) and the probabilities of switching from one state to another (transition probabilities). Emission probabilities were chosen to reflect observations previously made in studies that tested for ovulation with LH tests or ultrasounds (6, 8, 16), while transition probabilities were chosen in a quasi-uniform manner (SI). We found that the ovulation estimations were robust to changes in transition probabilities but not to variations in emission probabilities (Fig S5, SI), indicating that this simple framework is suitable to detect ovulations in cycles of any length, and potentially including pregnancies, relying primarily on users' observations.

Once the model was defined, we used the Viterbi and the Backward-Forward algorithms (27) to calculate the most probable state sequence for each cycle (SI) and thus to have an estimation of ovulation timing, i.e. the most likely day of the cycle in which the HMM is in the state "ovulation". We also computed the uncertainty of the estimation, *i.e.* the standard deviation of the distribution of probabilities for the state 'ovulation', which can be interpreted as the confidence interval in days for the time of ovulation estimation (SI). We also defined a

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confidence score that accounts for missing observations and variation in temperature taking time in a window of ~5 days around the estimated ovulation day (SI).

HMM states

We defined 10 states as a discretization of the hormonal evolution across the cycle (further details in SI)

HM: onset of the menses and the heavy/medium flow of fresh blood.

LM: days of light bleeding or spotting that conclude menstruations.

LE: Low Estrogen.

HE: High estrogen (HE

Ovu: Ovulation

Rise: Temperature rise associated with rise in progesterone production.

HP: High Progesterone

EP: Estrogen Peak in luteal phase.

LP: Low Progesterone.

End: Artificial state for the end of each cycle.

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Author contributions:

L.S. initiated and conceived the study, analyzed the data and designed the figures, L.S., K.W., P.H. and M.S. wrote the manuscript. All authors discussed the results and implications and commented on the manuscript at all stages.

Competing interests:

L.S., K.W. and M.S. have no competing interest. P.H. discloses that she is a consultant and medical advisor to Clue by Biowink.

Data and materials availability:

While the privacy policies and terms of usage of the two apps allow the sharing of their de-identified users' data with third parties for research purposes, they do not allow public sharing of

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the raw datasets. Aggregated values necessary for the production of the figures are available at https://github.com/lasy/menstrual_health_FAM[1].

[1] This repository is currently private and will be made public at publication. The datasets have been submitted as a compressed zip file together with this manuscript.

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Figures and figure legends

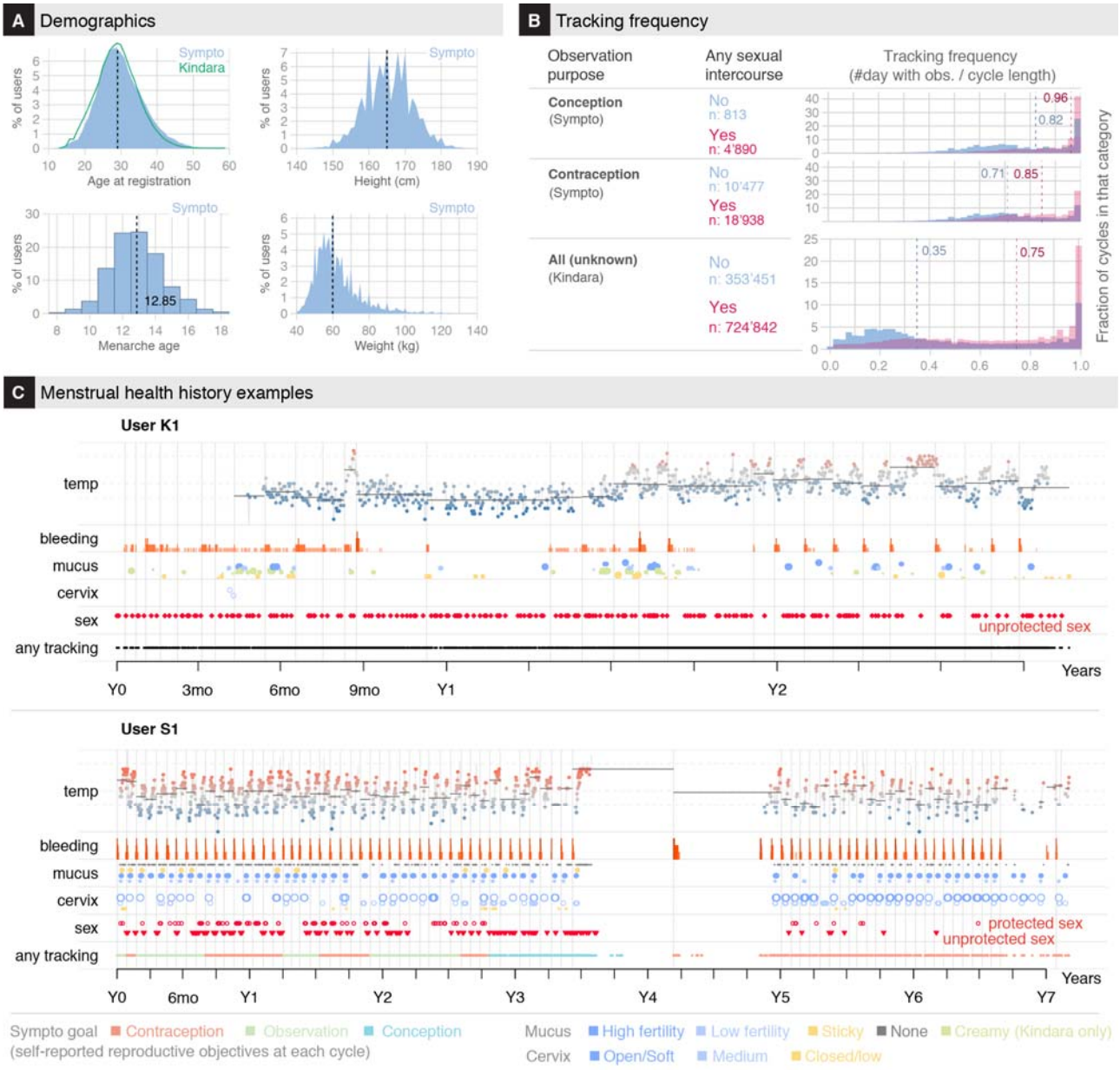

Figure 1: Demographics and tracking behavior of users

(A) Users' age at registration (top-left), reported height (top-right), weight (bottom-right) and menarche age of users.

(B) Cycle-specific tracking frequencies (top: Sympto, bottom: Kindara). 39,896 (Sympto) + 719,182 (Kindara) *standard cycles* were used (Methods). Dashed lines indicate median values.

(C) Menstrual history of two long term Kindara (top) and Sympto (bottom) users. Time is shown in years as relative

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to the first observation of each user. Top user is seeking to achieve pregnancy and show a long anovulatory episode during which her overall temperature profile is lower. She returns to more regular, ovulatory cycles in her last year of tracking, as indicated by the bleeding frequency and the temperature profiles. The bottom user has used the app to avoid pregnancy and observe her cycle for almost 3 years, before trying to conceive, which she likely achieves after 9 cycles (her reported reproductive objective switches from “contraception” to “conception” – line “any tracking” at the bottom). 9 months later, the user reports bleeding, which likely indicates post-partum bleeding (lochia). After another 9 months, probably as she stops breastfeeding, she logs menstrual observations and returns to using the app to avoid pregnancy.

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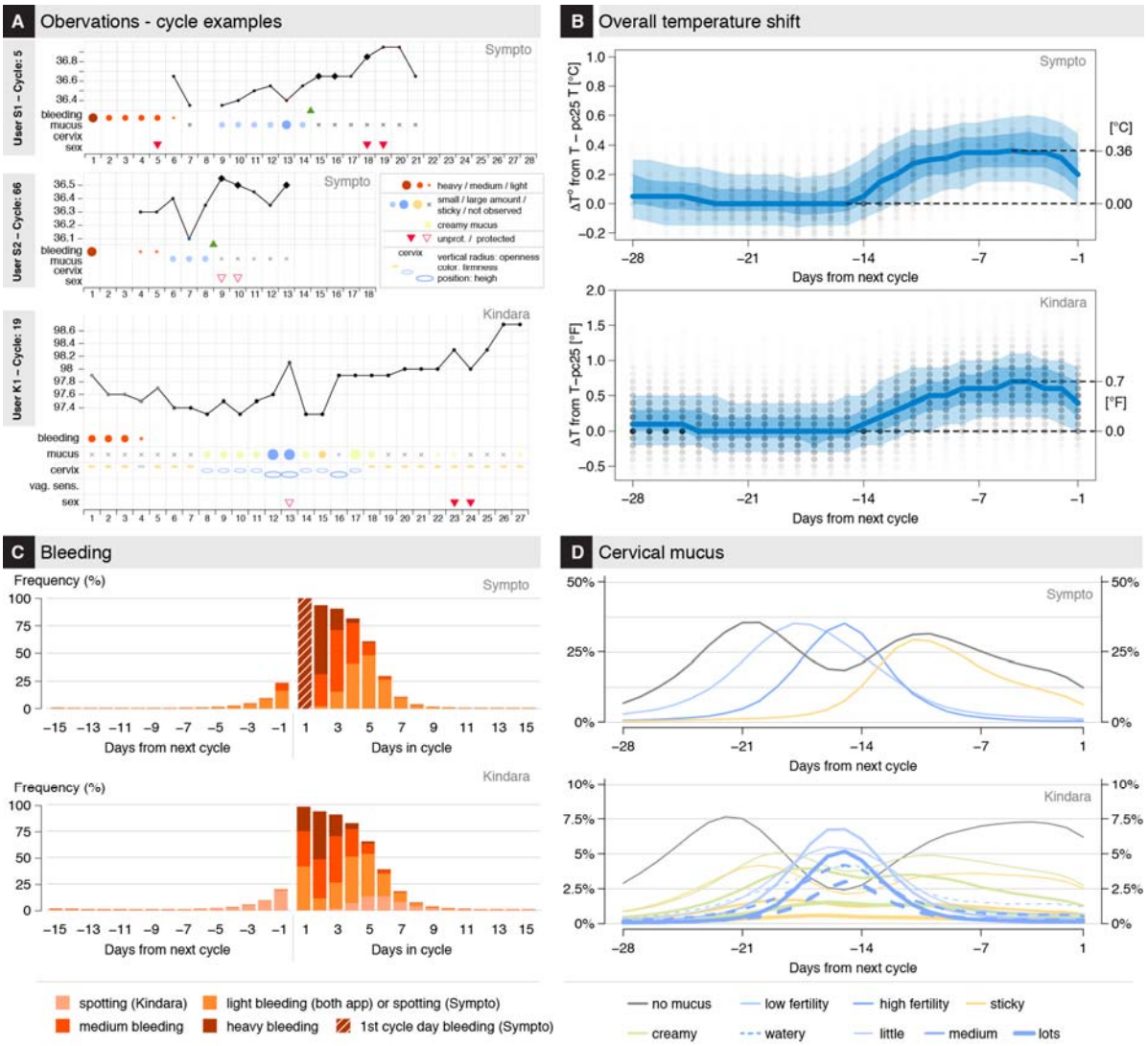

Figure 2: User observations overview

(A) Examples of observations: the 5th tracked cycle (top) and 66th cycle (middle) cycle of two different Sympto users. Observations of the 19th cycle (bottom) of a Kindara user.

(B) ΔBBT (variation from the 25% percentile of temperature in this cycle) values are shown on each day of the cycle, from the end of the cycle. Opacity of the dots reflects the number of observations. The median value: thick blue line. 10, 25, 75 and 90 percentiles of ΔBBT:

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translucent blue bands.

(C) Frequency of bleeding observations, for the end (left) and beginning (right) of cycles. The Sympto app only starts a new cycle on the first recording of heavy bleeding (score 3/3, dark red) after a post-ovulatory infertile phase, thus all cycles present heavy bleeding at the start of the cycle (hashed dark red bar).

(D) Frequency of cervical mucus observations from the end of cycles (top: S, bottom: K). (Kindara) Little quantity of watery mucus (dashed line) and little or medium quantity of egg-white like mucus (solid line) are considered as 'low fertility' mucus (light blue) while large quantities of egg-white like and medium or large quantities of watery mucus are considered as 'high fertility' mucus (dark blue) (B-D) 39,896 (S) + 719,182 (K) *standard cycles* were used (Methods)

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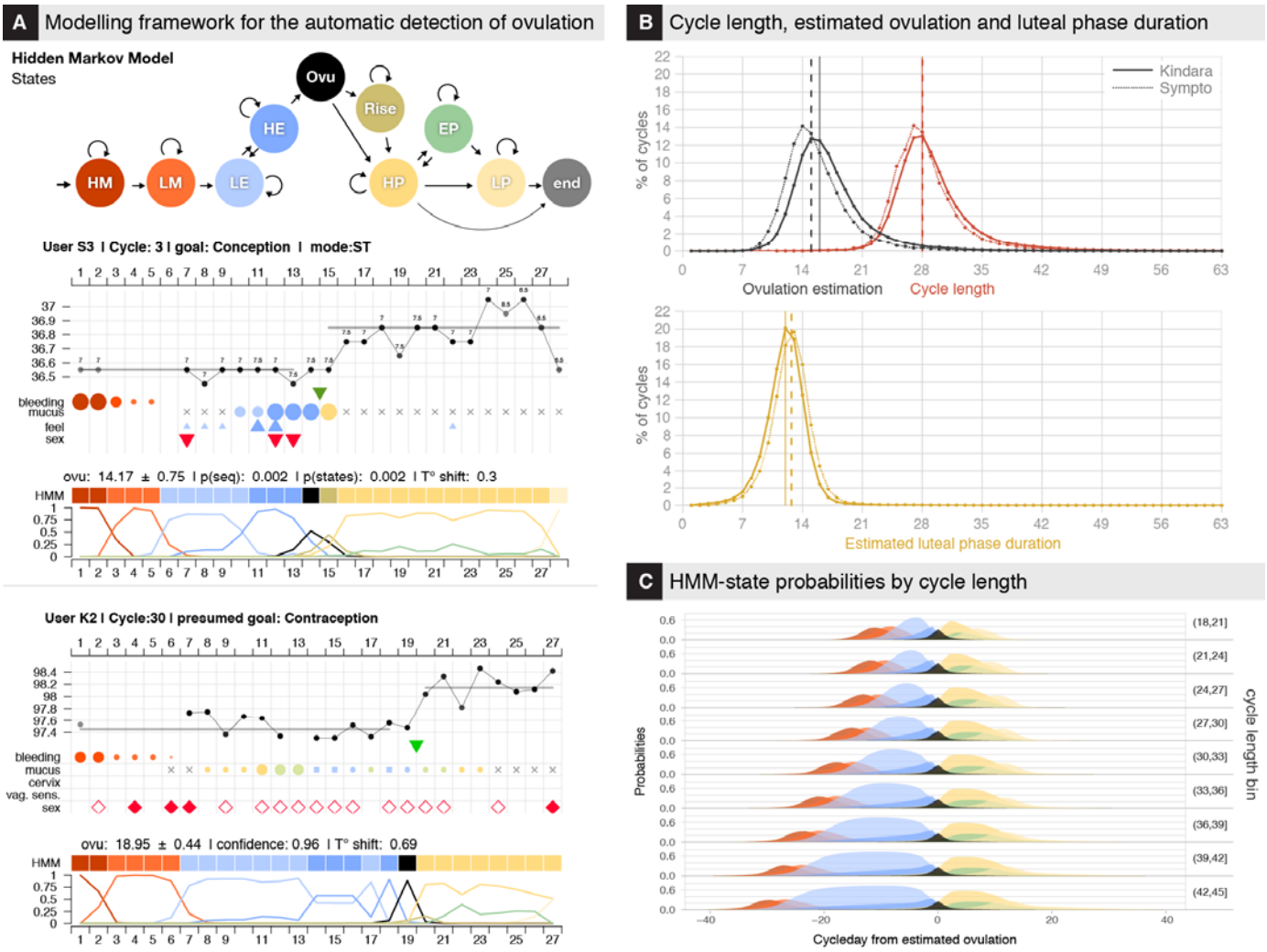

Figure 3: Modeling framework for the estimation of ovulation and menstrual states

(A) Modeling framework for the estimation of ovulation timing. (Top) Schematics of the 10-states HMM which discretizes the menstrual hormonal events (HM: Heavy Menses, LM: Light Menses, LE: Low Estrogen, HE: high Estrogen, Ovu: Ovulation, Rise: progesterone/BTT Rise, HP: High Progesterone, EP: Estrogen Peak in luteal phase, LP: Low Progesterone). Arrows indicate possible state-transition; arrow thickness is not representative of actual transition probabilities (Methods). (Bottom) Examples of menstrual state estimation for the 2rd and 3rd cycle of 2 users. (Top of each chart) Original user observations as in Fig. 2A. (Middle of each chart) Colored squares HMM-labeled line) represent the most likely sequence of HMM states given the observations (Methods). (Bottom of each chart) Normalized probabilities of each state on each day of the cycle (Methods).

(B) (Top) Cycle length and estimated ovulation day. (Bottom) Luteal phase duration, computed as the number of

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days between the ovulation day (excluded) and the1st day of the next cycle (excluded). Vertical lines indicate median values. 80,708 (K) + 24,119 (S) *cycles with reliable ovulation estimation* were used (Methods).

(C) Average estimated state probabilities by cycle-day counting from estimated ovulation aggregated by total cycle length (in bins of 3 units) for all *cycles with reliable ovulation estimation.*

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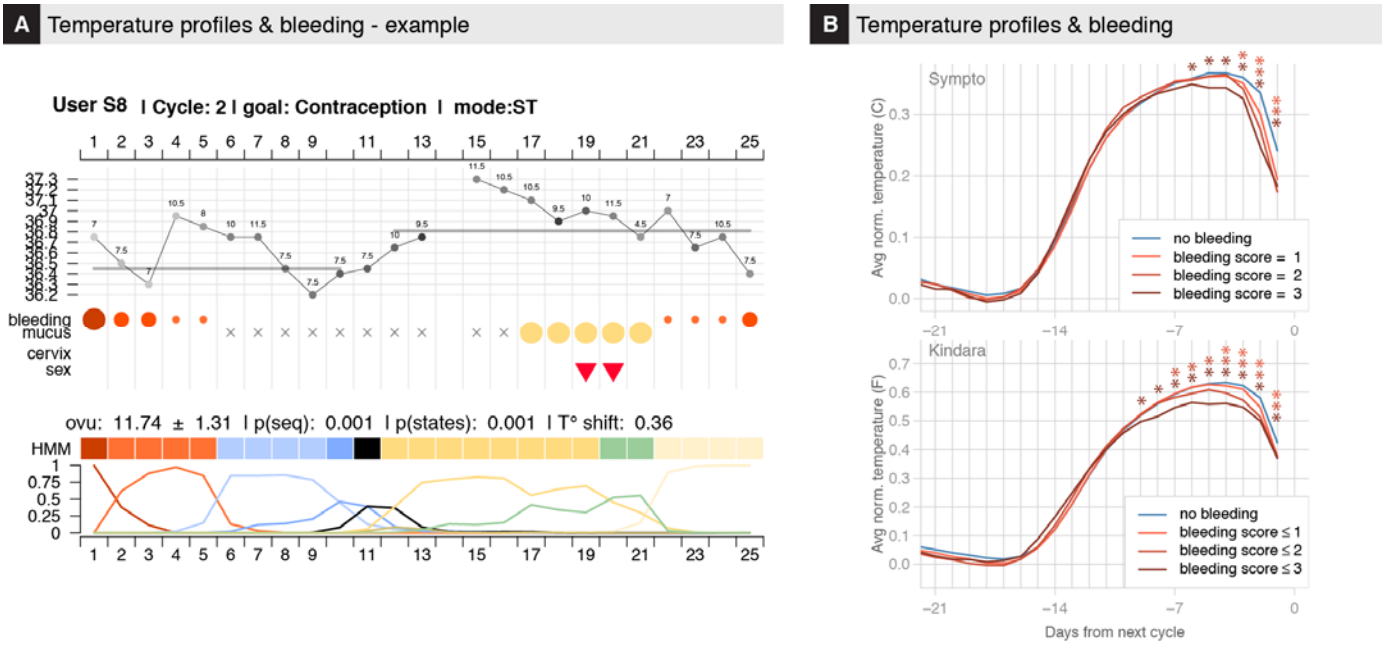
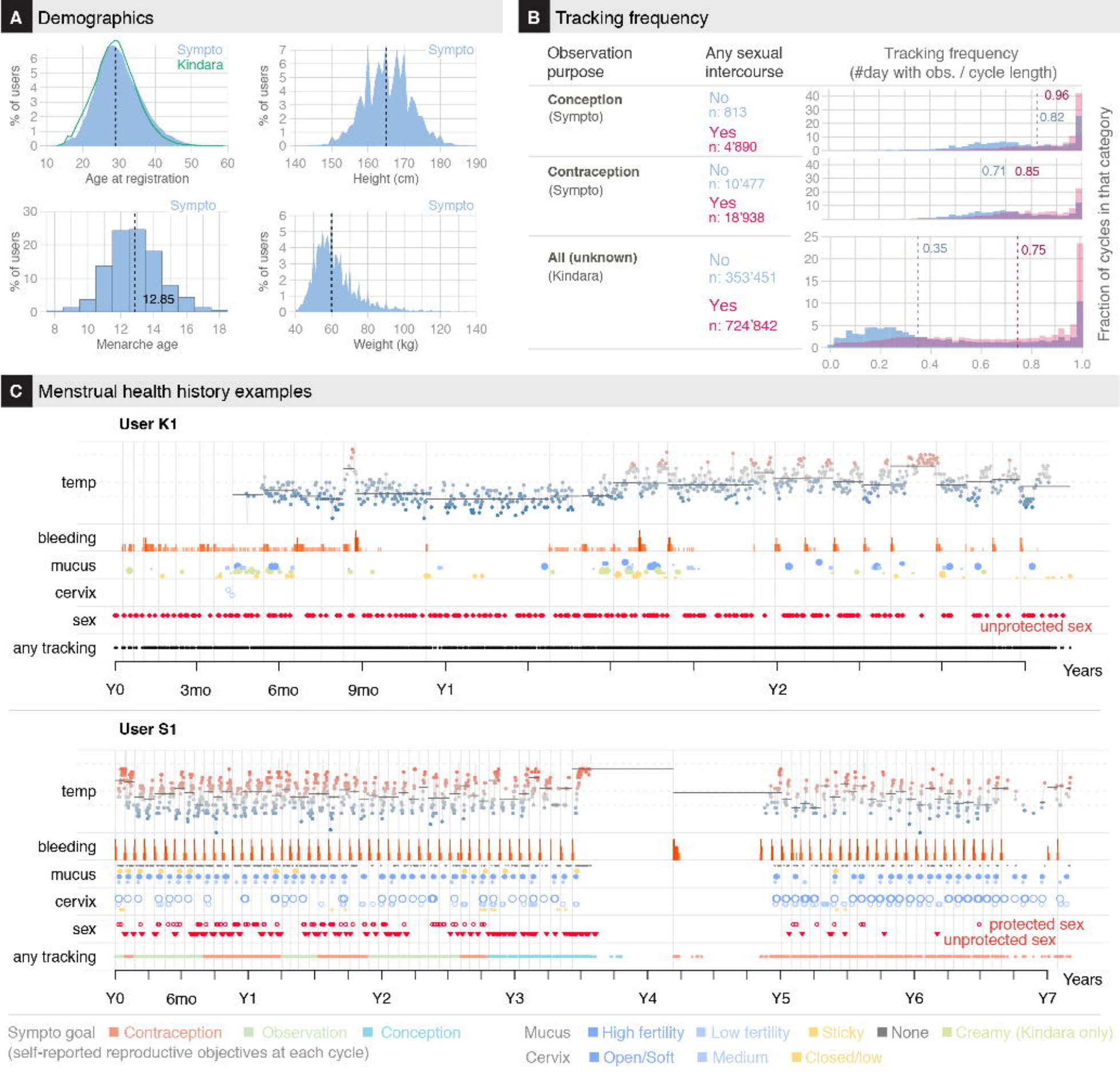
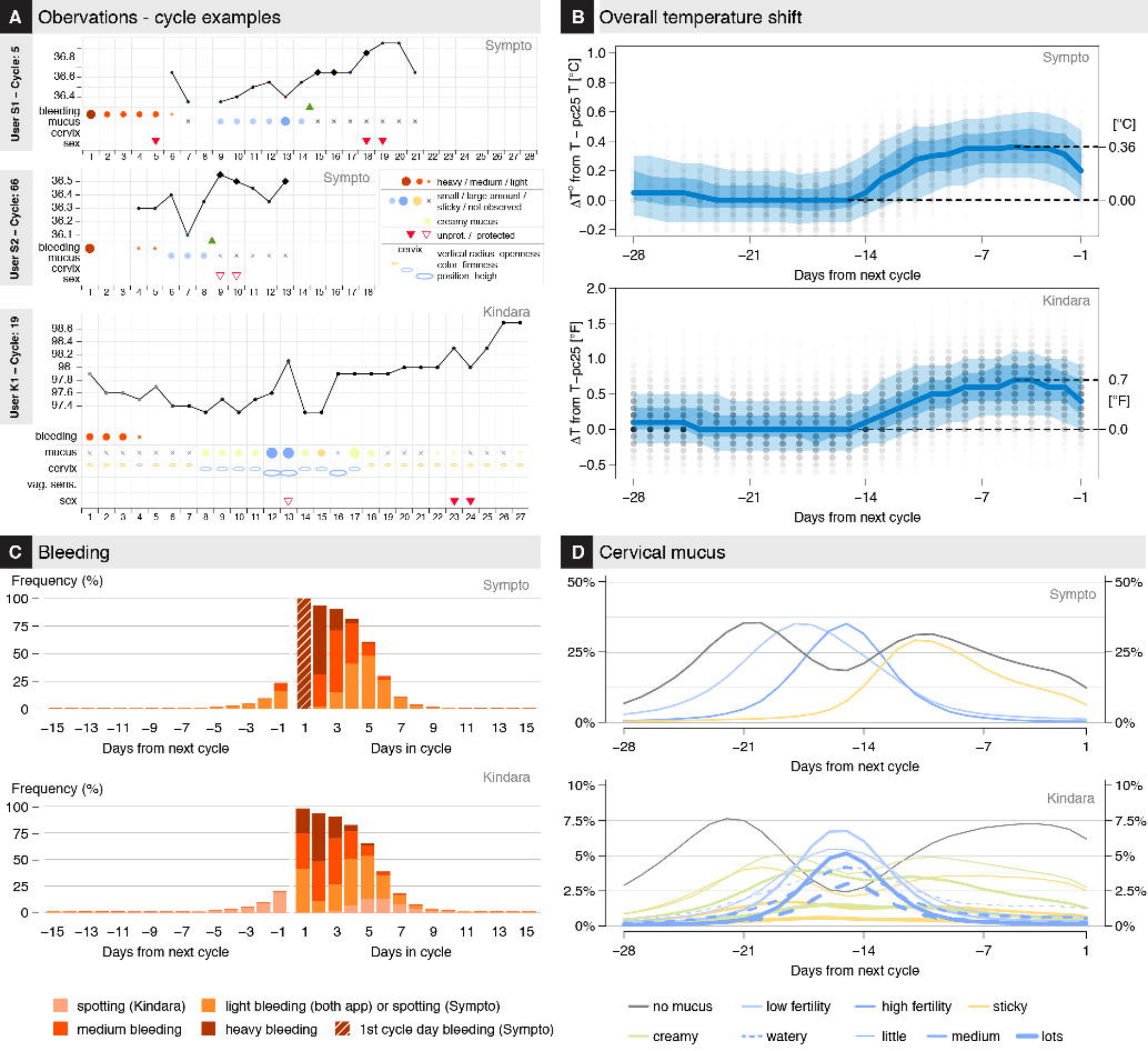


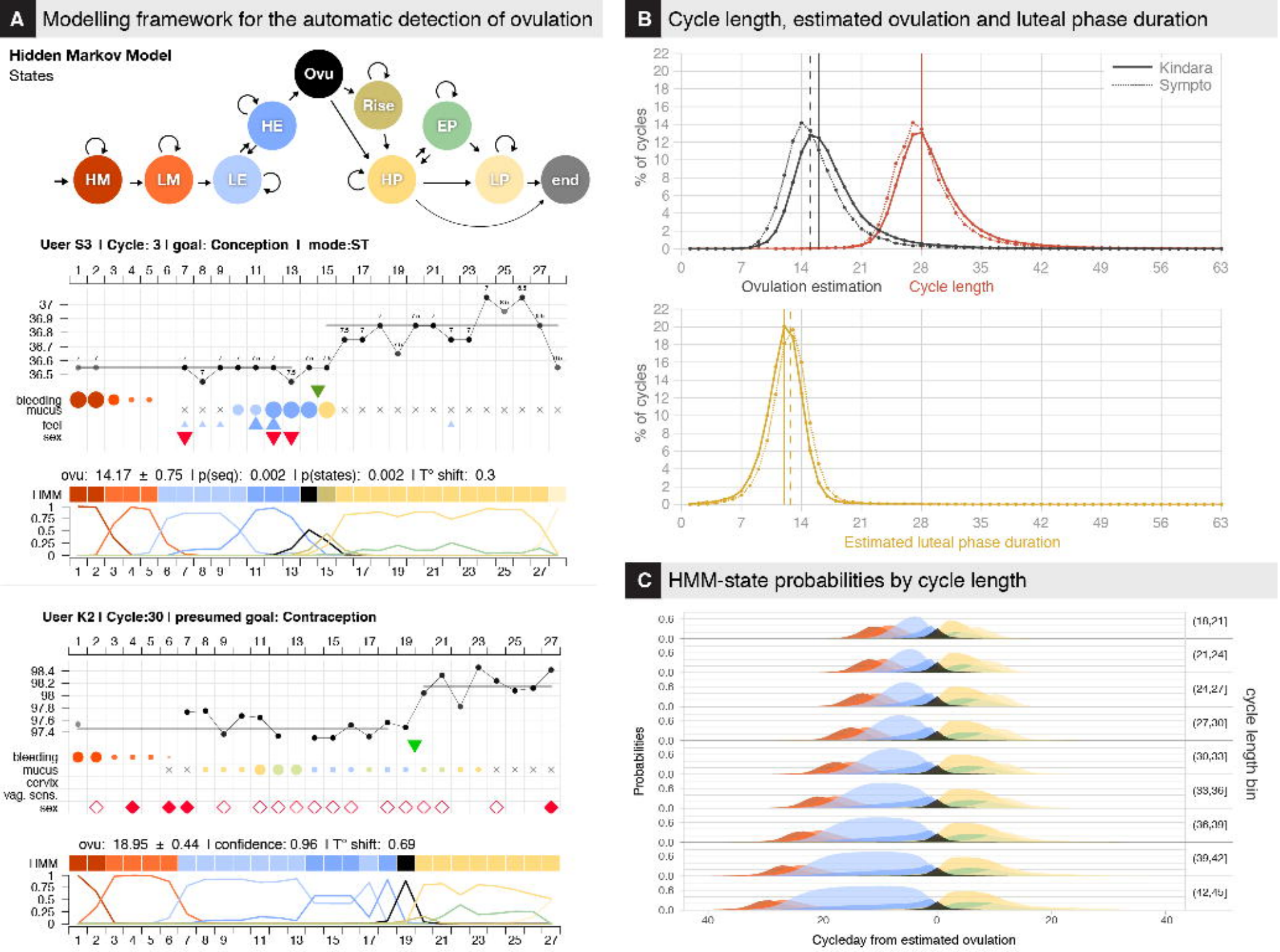
Figure 4: Temperature profiles and bleeding at the end of cycle

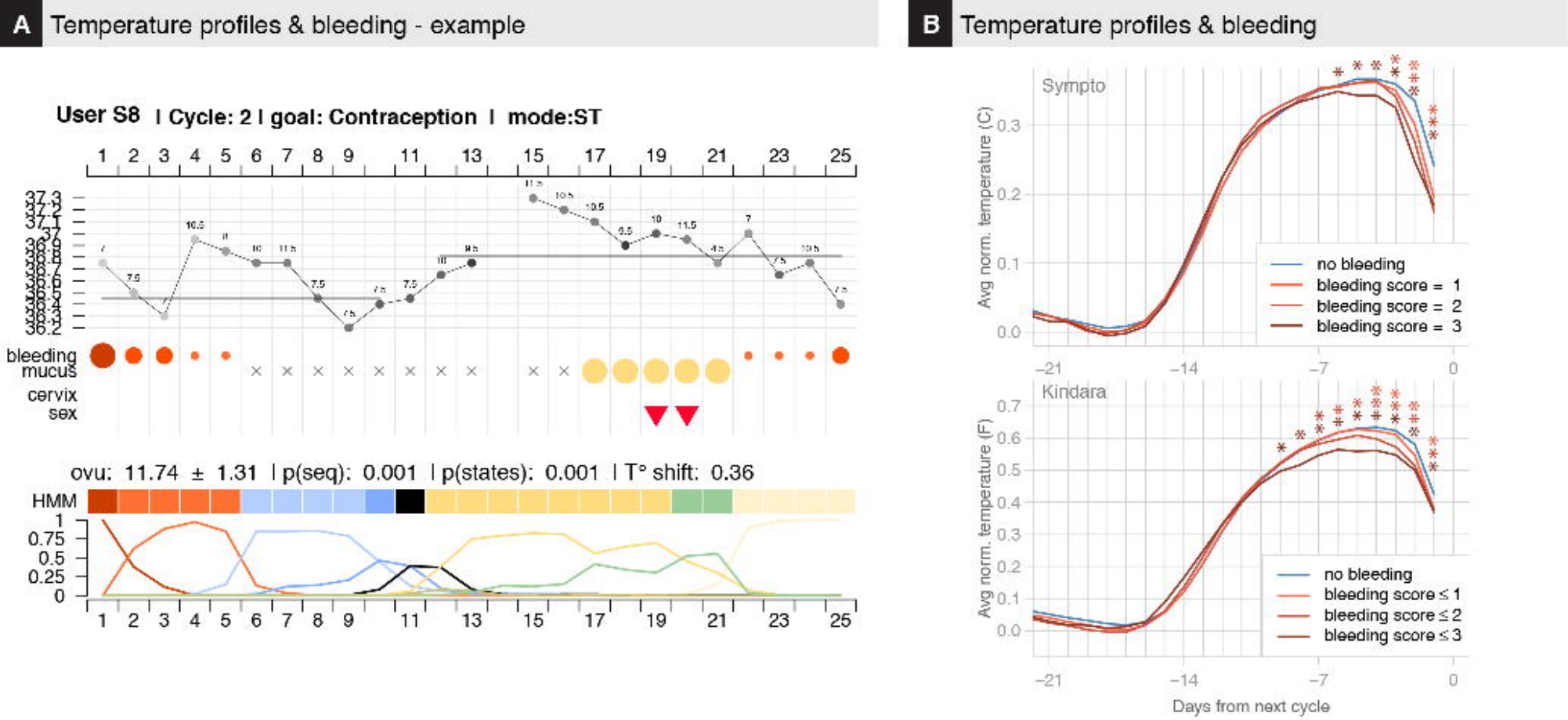
(A) 2nd cycle of a user with an estimated ovulation on day 11, exhibiting a slow temperature decrease throughout the luteal phase (top) and corresponding HMM most likely states and probabilities (bottom).

(B) Average normalized temperature profiles for cycles in which no (blue), light (light red), medium (medium red) or heavier (dark red) bleeding was observed at the end of cycles. Bleeding score is computed as the sum of reported bleeding within the last 10 days of the cycle (spotting = 0.5 in Kindara). Temperature is normalized by the 25% lowest percentile of that cycle (as in Fig 2B). Stars indicate significant differences in distributions between the 'no bleeding' group and the bleeding groups (t-test, $p < 0.05$, bleeding group colors).


A Demographics
Sympto
Kindara
% of users
Age at registration
Height (cm)
Menarche age
12.85
Weight (kg)
B Tracking frequency
Observation purpose
Any sexual intercourse
Tracking frequency (#day with obs. / cycle length)
Conception (Sympto)
No n: 813
Yes n: 4'890
0.96
0.82
Contraception (Sympto)
No n: 10'477
Yes n: 18'938
0.71
0.85
All (unknown) (Kindara)
No n: 353'451
Yes n: 724'842
0.35
0.75
Fraction of cycles in that category
C Menstrual health history examples
User K1
temp
bleeding
mucus
cervix
sex
any tracking
unprotected sex
Years
Y0
3mo
6mo
9mo
Y1
Y2
User S1
protected sex
unprotected sex
Y3
Y4
Y5
Y6
Y7
Sympto goal
Contraception
Observation
Conception
(self-reported reproductive objectives at each cycle)
Mucus
High fertility
Low fertility
Sticky
None
Creamy (Kindara only)
Cervix
Open/Soft
Medium
Closed/low


A
Obervations - cycle examples
User S1 – Cycle: 5
Sympto
bleeding
mucus
cervix
sex
User S2 – Cycle: 66
Sympto
heavy / medium / light
small / large amount / sticky / not observed
creamy mucus
unprot. / protected
cervix
vertical radius openness
color firmness
position height
User K1 – Cycle: 19
Kindara
bleeding
mucus
cervix
vag. sens.
sex
B
Overall temperature shift
Sympto
ΔT° from T – pc25 T [°C]
[°C]
0.36
0.00
Days from next cycle
Kindara
ΔT from T–pc25 [°F]
0.7
[°F]
0.0
Days from next cycle
C
Bleeding
Frequency (%)
Sympto
Days from next cycle
Days in cycle
Kindara
Frequency (%)
Days from next cycle
Days in cycle
spotting (Kindara)
light bleeding (both app) or spotting (Sympto)
medium bleeding
heavy bleeding
1st cycle day bleeding (Sympto)
D
Cervical mucus
Sympto
Days from next cycle
Kindara
Days from next cycle
no mucus
low fertility
high fertility
sticky
creamy
watery
little
medium
lots


A
Modelling framework for the automatic detection of ovulation
Hidden Markov Model
States
Ovu
Rise
HE
EP
HM
LM
LE
HP
LP
end
User S3 | Cycle: 3 | goal: Conception | mode:ST
bleeding
mucus
fcol
sex
ovu: 14.17 ± 0.75 | p(seq): 0.002 | p(states): 0.002 | T° shift: 0.3
IMM
User K2 | Cycle:30 | presumed goal: Contraception
bleeding
mucus
cervix
vag. sens.
sex
ovu: 18.95 ± 0.44 | confidence: 0.96 | T° shift: 0.69
IMM
B
Cycle length, estimated ovulation and luteal phase duration
Kindara
Sympto
% of cycles
Ovulation estimation
Cycle length
% of cycles
Estimated luteal phase duration
C
HMM-state probabilities by cycle length
Probabilities
cycle length bin
Cycleday from estimated ovulation


A
Temperature profiles & bleeding - example
User S8 | Cycle: 2 | goal: Contraception | mode:ST
bleeding
mucus
cervix
sex
ovu: 11.74 ± 1.31 | p(seq): 0.001 | p(states): 0.001 | T° shift: 0.36
HMM
B
Temperature profiles & bleeding
Sympto
Avg norm. temperature (C)
no bleeding
bleeding score = 1
bleeding score = 2
bleeding score = 3
Kindara
Avg norm. temperature (F)
no bleeding
bleeding score ≤ 1
bleeding score ≤ 2
bleeding score ≤ 3
Days from next cycle