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Associations between physical exercise patterns and pain symptoms in individuals with endometriosis: a cross-sectional mHealth-based investigation

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ABSTRACT

Objectives This study investigates the association of daily physical exercise with pain symptoms in endometriosis. We also examined whether an individual's typical weekly (ie, habitual) exercise frequency influences (ie, moderates) the relationship between their pain symptoms on a given day (day *t*) and previous-day (day *t-1*) exercise.

Participants The sample included 90 382 days of data from 1009 participants (~85% non-Hispanic white) living with endometriosis across 38 countries.

Study design This was an observational, retrospective study conducted using data from a research mobile app (Phendo) designed for collecting self-reported data on symptoms and self-management of endometriosis.

Primary outcome measures The two primary outcomes were the composite day-level pain score that includes pain intensity and location, and the change in this score from previous day (Δ-score). We applied generalised linear mixed-level models to examine the effect of previous-day exercise and habitual exercise frequency on these outcomes. We included an interaction term between the two predictors to assess the moderation effect, and adjusted for previous-day pain, menstrual status, education level and body mass index.

Results The association of previous-day (day *t-1*) exercise with pain symptoms on day *t* was moderated by habitual exercise frequency, independent of covariates (rate ratio=0.96, 95% CI=0.95 to 0.98, p=0.0007 for day-level pain score, B=−0.14, 95% CI=−0.26 to −0.016, p=0.026 for Δ-score). Those who regularly engaged in exercise at least three times per week were more likely to experience favourable pain outcomes after having a bout of exercise on the previous day.

Conclusions Regular exercise might influence the day-level (ie, short-term) association of pain symptoms with exercise. These findings can inform exercise recommendations for endometriosis pain management, especially for those who are at greater risk of lack of regular exercise due to acute exacerbation in their pain after exercise.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ This study leverages data from a research mobile app (Phendo) designed for collecting self-reported data on symptoms and self-management of endometriosis.
- ⇒ Daily exercise and pain symptom patterns in endometriosis are investigated under ecologically valid conditions.
- ⇒ The participant sample (N=1009) represents 38 countries, ages across the reproductive life span and various person-level characteristics.
- ⇒ The study is limited by self-reported data collection by somewhat consistent trackers and lacks details on duration or intensity of exercise to evaluate as potential moderators.
- ⇒ Participants consisted of mostly non-Hispanic white individuals; therefore, results might not be generalisable to other demographic groups.

INTRODUCTION

Exercise, a subset of physical activity (PA) that is planned, structured, repetitive and intended to improve or maintain physical fitness, is an important component of effective pain management (ie, reduction and prevention of pain symptoms).[1 2] Both acute (ie, single bout/session) and chronic (ie, repeated bouts/sessions over time) exercise training have been demonstrated to improve numerous pain-related conditions.[1 3–7] However, pain-related responses to exercise are variable in populations with chronic pain conditions.[8] Similarly, exacerbation of pain with exercise could pose a barrier to regular exercise in such individuals, thus increasing resistance to exercising, which in return can worsen pain, related disability and risk of comorbidities.[9–11] Investigation into the naturally occurring pattern of pain symptoms associated with exercise behaviour can help inform the design of exercise-based therapies for targeting disease-related pain symptoms.

Individuals with endometriosis may benefit from such investigations for several reasons.[12–14] Endometriosis is a systemic, oestrogen-dependent inflammatory condition characterised primarily by chronic pelvic and abdominal pain, pain with sexual intercourse and infertility.[15,16] It significantly impacts daily function and quality of life (QoL),[17,18] contributing to a productivity loss of 6.3 hours/week[19] and an estimated $69.4 billion in excess health expenditures annually in the USA.[18] Existing medical and hormonal therapies have limited efficacy for pain management, often confounded by side effects.[20] Opioids and other analgesics are commonly prescribed for long-term use,[21,22] despite treatment guidelines recommending use of non-pharmacological therapies including PA.[23] Consequently, there is a critical need to identify alternative approaches for endometriosis pain management.

One such approach is exercise, based on various mechanisms proposed in the literature[24] that might pertain to endometriosis. These include regulation of the serotonergic and opioid receptors,[25] reduction of inflammatory markers associated with pain[26,27] and effect of exercise on nerve growth factor expression that is associated with the painful endometriosis lesions.[28,29] Exercise can increase pain management self-efficacy, which is associated with improved pain outcomes and QoL, for individuals with chronic pain.[30] While the evidence on exercise for pain management is promising,[4,31,32] existing data are scarce, cross-sectional and indicate variable effects on pain outcomes.[32–36] Despite these limitations, previous reports of exercise-induced adaptations to pain stimuli through increased pain threshold suggest that the regularity with which an individual engages in exercise over the long term (ie, habitual exercise frequency) might influence (ie, moderate) the relationship between their day-level exercise and pain symptoms.[37,38] Among regular exercisers, pain-related activation has been demonstrated in the brain's descending antinociceptive pathway, with corresponding reductions in self-reported pain after acute bouts of at least moderate-intensity exercise.[39] Moreover, studies report that habitual exercise frequency moderates a variety of self-reported outcomes (eg, mood, anxiety, fatigue) in response to acute exercise.[40–42] While these findings are promising, their generalisability is limited by sample characteristics, laboratory-based experimental pain stimuli and exercise manipulations, and brief measurement duration of up to several hours. Thus, further investigation is needed to examine the relationship between pain symptoms and exercise behaviour with a representative sample, under ecologically valid conditions, while accounting for possible between-individual variability and temporal lags in the outcome that extend beyond several hours.

Accordingly, this study examines the naturally occurring daily patterns of pain symptoms and exercise behaviour in endometriosis. We leverage mobile self-tracking, a particularly useful approach for capturing ecologically valid profiles of the dynamic temporal fluctuations and between-individual variability in pain over time.[43] We primarily aim to delineate the degree to which an individual's typical weekly exercise frequency (ie, habitual exercise) influences (ie, moderates) the association of their pain symptoms on a given day (day *t*) with their previous-day (day *t-1*) exercise behaviour (ie, lagged-day effects). Given the previously documented variable course of pain symptomatology in endometriosis,[44] we also delineate the variability in day-to-day pain experiences within these analyses.

MATERIALS AND METHODS

Study design

This study was conducted with retrospective data collected through the observational research mobile app 'Phendo'. Phendo was designed and developed for self-tracking endometriosis symptoms and its management. It is available for iOS (available at https://itunes.apple.com/us/app/phendo/id1145512423) and Android (available at https://play.google.com/store/apps/details?id=com.appliedinformaticsinc.phendo) in App stores for free.

Study sample and inclusion criteria

The study sample comprised Phendo users with a self-reported surgery, clinician or suspected diagnosis of endometriosis and self-tracked exercise and pain data between November 2016 and April 2020. All participants, regardless of diagnosis type, are provided the same set of measures for completion in the app. In a previous study, the endometriosis phenotype (ie, characterisation) obtained using Phendo data was consistent with both the characterisation of the disease in the literature based on standard clinical surveys and clinician (ie, human expert) evaluations.[45] We decided a priori to include all participants who selected one of the three affirmative responses in the present analyses, excluding those who indicated that they did not have endometriosis. Out of the initial eligible pool of 9792 Phendo users with reported endometriosis, 7949 had at least 1 day of tracking of the variables of interest for the study. Of these, 1009 users had sufficient amount of data on pain and exercise for analysis (see the Data analysis section) and were included in the study.

Recruitment and informed consent

Study participants were passively recruited through one of the App stores, engagement on study social media sites or word of mouth. Upon downloading Phendo, all potential users went through an informed consent and enrolment process before tracking any data. First, they were provided with an explanation of the app, its overall purpose and link to its website (citizenendo.org) which includes detailed information and instructional videos for using the app. Participants completed a brief 'verify your understanding' quiz to ensure their comprehension of how their data might be used for research purposes, anonymity and confidentiality (see online supplemental figures 1 and 2 for example screenshots). This was followed by formal electronic informed consent (and assent for individuals 13–18 years old), a copy of which was sent to the participant. Once enrolled, users were instructed to track daily, but they were free to track as much or as sporadically as they wished, and they did not receive any prompts or requests to track a specific variable from the research team. Findings from a previous study evaluating recruitment and retention patterns within Phendo and seven other similar self-tracking apps indicated that Phendo's user engagement was similar to standard engagement patterns in research smartphone apps.[46] Participants in the current study did not receive financial compensation for their tracking activities.

Study measures

Day-level pain

We assessed day-level pain through multiple items within Phendo: (1) 'Are you in pain now? Where is the pain?', (2) 'Any gastrointestinal or urinary issues?' (painful urination (dysuria), painful bowel movement (dyschezia)). Phendo pain item response options include all areas of the body (20 available choices, as well as right/left and upper/middle/lower specification), and can be mapped onto a visual, analogous to the McGill Pain Scale.[47] Pain severity for each affirmative response was rated on a 3-point categorical scale (mild, moderate or severe), analogous to other commonly used pain rating scales in the literature.[48 49] This categorisation has been used for standardisation and comparisons across different pain measures, and demonstrated superior ability to capture the non-linear relationship between reported pain severity and interference with activity than use of numbers.[50 51]

We computed a heuristic, composite day-level pain score to capture participants' conceptualisation of their pain experience by summing the severity scores reported for each body area (eg, moderate pain in abdomen, mild pains in chest and leg would yield *2+1+1=4* as the total score).[44] This allowed consideration of the multidimensional pain experience in a single outcome. To account for and circumvent any potential pain rumination/catastrophising[52 53] and varying tracking habits among participants, the score was computed based on the unique reports of area–severity pairs per day for each participant (eg, if a participant tracked mild abdominal pain three times in a day, this abdomen–mild pair is counted toward the daily pain score only once). This score was the foundation of two study outcome variables: (1) total day-level pain score, and (2) difference in day-level pain score from previous day to the next (ie, $t-(t-1)$). The latter captures additional nuances in the data, enabling analyses to distinguish between participants with overall high day-level pain scores over time and experience a post-exercise reduction in pain versus those with low pain scores and who do not experience a post-exercise reduction in pain. In the current study sample, the composite pain scores were moderately correlated with scores from other standard pain measures (eg, r=0.36, p<0.0001 with the Pelvic–Abdominal Pain Visual Analog Scale (VAS); r=−0.46, p<0.0001 with Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36) Bodily Pain subscale).

Day-level and habitual exercise

Phendo allows tracking of daily exercise through responding to a root question 'Did you exercise today? (Yes/No)'. Upon selecting a 'Yes', users can further customise their entry within this item by adding exercise details through unrestricted free-text responses. We used responses to the root item to compute day-level and mean weekly exercise frequency (ie, habitual exercise) for each participant. We calculated the latter by summing the number of exercise reports tracked per week across the range of days of data and then dividing this number by the total number of weeks of data. We used free-text responses to categorise exercises by modality and to validate that the entries were exercise related. Any non-exercise activity (eg, sleep, meditate, sitting, socialise) was recoded as a no exercise in the analytical data set. This day-level exercise assessment aims to increase ecological validity[54 55] and reduce the likelihood of low test–retest reliability and inaccuracy due to recall bias.[56] We evaluated the validity of the scores from the Phendo exercise item through a series of analyses with the study sample.[57] Results supported its concurrency with other self-reported recall-based measures (ie, Kendall's τ=0.256, p<0.001 with Exercise Vital Sign[58] and τ=0.294, p=0.001 with accelerometers; B=18.73, p=0.039 in association to the Nurses' Health Study II (NHS-II) Weekly Exercise Scale[59] scores).

Standard pain and exercise measures

To allow comparisons of the study sample with others in the literature, we report sample summary scores from the following components of the World Endometriosis Research Foundation Endometriosis Patient Questionnaire[60 61] : (1) the two-item Bodily Pain subscale of the SF-36,[62] (2) Pelvic–Abdominal Pain VAS ('Please rate how severe your general pelvic/lower abdominal pain was at its worst in the last 3 months using the pain scale below where 0=no pain and 10=worst imaginable pain.'), and (3) the eight-item NHS-II Weekly Physical Activity Scale.[59] It measures self-reported weekly duration of major exercise modalities (ie, walking, running, lap swimming, jogging, bicycling, tennis, callisthenics, other aerobic recreation) in a typical week in the past 12 months. The duration can further be multiplied by their metabolic equivalents based on the Compendium of PA[63] and summed to obtain the total weekly exercise-related energy expenditure (EE). We report both the total weekly minutes and EE for the sample.

Patient and public involvement

We developed Phendo measures using patient-centred participatory design, through qualitative (focus groups, interviews) and quantitative research (surveys, coded content analysis) with participants with endometriosis, described in detail elsewhere.[64 65] This technique for developing patient-reported outcome measures has been suggested to enhance content validity and relevance of the measure to the target population, thus providing a more comprehensive and accurate representation of the disease under study.[54 66–68]

Data analysis

Sample characteristics

We characterised the study sample through frequencies (%) and means (SD) of demographics, self-reported pain medication use, and scores on the standard pain and exercise measures for those who completed the surveys. We characterised pain symptomatology in the sample by describing the prevalence of self-tracked pain severities by each body area.

Associations of pain symptoms with exercise behaviour

Using generalised linear mixed models (GLMMs), we separately estimated day-level total pain score and pain score difference as primary outcomes. Both outcomes were regressed on previous-day (day *t-1*) exercise and mean weekly exercise frequency to estimate the slope of mean pain level on day *t* and change in pain. We included an interaction term between the two predictors to assess the moderation of the day-level association by each individual's mean weekly exercise frequency. We included participant as a random effect to account for between-person variability in daily pain by estimating a separate intercept for each participant. Models were further adjusted for menstrual status (binary: yes/no), previous-day (ie, day *t-1*) pain, body mass index (BMI) and education level. Race/ethnicity and age were not significantly associated with average daily pain reports (F=1.68, p=0.14 for race/ethnicity; r=−0.148, p=0.07 for age), and age was further significantly associated with education level (Kruskal-Wallis X^2=64.948, p<0.0001). To avoid redundancy and multicollinearity, race/ethnicity and age were not included as model covariates.

Model specification

We specified a zero-inflated negative binomial distribution when modelling the total pain outcome, as it has been demonstrated to provide the best fit for outcomes with overdispersion and zero inflation (ie, zeros due to both sampling and missingness).[69–71] Missing values in the BMI (22%), education level (19%) and menstrual status (22%) were imputed as described in online supplemental file 1 and checked for appropriateness based on convergence and marginal distributions following guidelines[72–74] (see online supplemental figures 3–5). Adequacy of imputations for valid statistical inference was verified based on the recommended measures of missing data information of fraction of missing information (λ) and relative increase in variance due to non-response (r)[75 76] (see online supplemental table 1). Further details of the model specification are in online supplemental file 1. We included participants who had at least 11 pairs of consecutive days of data in the final analytical sample as this provided sufficient amount of data to (1) ensure model convergence and improve reliability and accuracy of the estimates, particularly the random effects and their variances,[77–80] and (2) adequately infer participants' habitual exercise level by considering at least 3 weeks' worth of tracking to compute the weekly exercise frequency. Finally, as a post-hoc analysis, we tested the possible influence of type of endometriosis diagnosis by including this categorical variable in the two models described above. We conducted the data analyses using R[81] and the glmmTMB package for the GLMMs.[70 71] Statistical significance level was set at p<0.05 for all analyses.

RESULTS

Sample characteristics

Sample characteristics are provided in table 1. Participants (N=1009) had on average 89.6 days of data available for analysis (SD=62.8, range=22–841, IQR=31). Participants collectively represented 38 countries, with a wide age range (14–63 years), and varying education and employment status. Almost 70% (N=702) had laparoscopic confirmation of their diagnosis, 19.8% (N=200) had a clinician diagnosis and 10.6% (N=107) had suspected endometriosis (ie, 'I think I have endometriosis (know the symptoms, no doctor)'). Scores from the VAS, SF-36 and NHS-II scales are provided in table 2. The overall prevalence rates of non-prescription pain medication use, opioid-based medication use, opioid–paracetamol/acetaminophen combination medication use were 49.35%, 11.19% and 11.39%, respectively (see table 1).

Pain symptom patterns

Mean daily pain score was 4.48 (SD=7.11, range=0–79). Mean person-level daily pain score (ie, 'mean of means') was 4.82 (SD=4.57, range=0–34). Moderate intensity was the most frequently reported severity across all body areas (mean=49.3%, SD=22.2), and pelvic pain was the most prevalent area, followed by back pain and gastrointestinal pain (see figure 1).

Habitual exercise patterns

Mean weekly exercise frequency was 1.43/week (SD=1.54, range=0–6.87/week, IQR=2.21). The exercise frequencies were at least three times per week, 21.3% (N=215); one to two times per week, 40.2% (N=406); and no regular exercise, 38.5% (388). Prevalence of the 10 most frequently reported exercise modalities in the sample is depicted in figure 2. Walking was the most common modality, reported by 50.94% of the participants, followed by yoga (30.82%) and muscle strength/endurance training activities (24.38%). Yoga and stretching exercises were collectively reported by almost 45% of the sample.

Association of day-level pain with exercise

Tables 3 and 4 display results of the GLMMs estimating day-level total pain score and difference. Coefficients for the model interaction terms indicated a small but statistically significant moderation of previous-day exercise by habitual exercise frequency (rate ratio=0.96 for total pain score and −0.14 for pain score difference, p<0.05; see

Table 1 Study sample characteristics

Characteristic (N)	Mean (SD)/frequency (%)
Age (827)	31.0 (7.26), median=30.6 (MAD=7.41), range=14.3–62.9
BMI (787)	25.9 (6.98), median=24.1 (MAD=4.74), range=16.01–72.24
Type of endometriosis diagnosis	
Surgery (702)	69.57
Clinician (200)	19.82
Self-diagnosis (107)	10.60
Work environment	
Home (218)	26.42
Outside (570)	69.09
Unknown (221)	21.29
Living environment	
Rural (129)	15.27
Suburban (340)	41.21
Urban (363)	44.00
Unknown (161)	19.50
Relationship status	
Married/domestic partnership (442)	53.57
Separated/divorced (28)	3.39
Single/never married (310)	37.57
Unknown (229)	22.69
Education level	
College or higher (547)	66.30
High school graduate or less (74)	8.96
Some college (209)	25.33
Unknown (179)	17.70
Employment status	
Employed (541)	65.57
Not employed (120)	14.54
Student (129)	15.63
Unknown (219)	21.70
Race/ethnicity	
White, non-Hispanic (699)	84.72
Black, non-Hispanic (20)	2.42
Asian (22)	2.60
Native American (6)	0.72
Hispanic (38)	4.60
Other (51)	6.18
Unknown (173)	17.14
Country of residence	
USA (444)	44.00
UK (83)	8.22
Canada (75)	7.43
Australia (59)	5.84
Germany (38)	3.76
New Zealand (34)	3.36
Other (69)	6.83
Unknown (207)	20.51

BMI, body mass index; MAD, Median Absolute Deviation.

figure 3). Further inspection of this interaction indicated a mean typical exercise frequency of ~3 times/week as the point after which previous-day exercise began to be associated with favourable pain outcomes (eg, a decrease from the predicted mean score) on the following day, adjusted for other day-level and person-level factors (figure 3). On the other hand, those who exercised less frequently or none were more likely to report higher levels of pain and larger increases (or smaller decreases) in pain 1 day after an exercise bout compared with not having exercised the day before.

Variability in estimated pain scores

There was substantial between-person variability in average day-level pain scores, based on the statistically significant random effect of participant in the models (see tables 3 and 4, also depicted in figure 4). We quantified the significance of this random effect through a restricted likelihood ratio test (RLRT) based on simulations from the model sample distribution.[82 83] This yielded an observed likelihood ratio (RLRT=7183.3, p<0.0001), indicating substantial contribution of the random effect to the total model pain variance.

Post-hoc analyses

Inclusion of diagnosis type in the model did not have an influence on the results based on the non-significant B coefficients (p=0.48 and p=0.59 for pain score and p=0.70 and p=0.27 for difference in pain score). There were no differences across the three groups with respect to either daily total pain score or difference (χ^2=1415.1,

Table 2 Sample study scores on standard measures of pain and exercise

EPQ-S measures (N)	Mean (SD)
SF-36 Bodily Pain (375)	35.47 (22.33)
Pelvic–Abdominal Pain VAS (316)	7.37 (1.97)
NHS-II PA Scale total weekly minutes (359)	175.2 (280.2)
NHS-II PA Scale total weekly EE (359)	16.13 (30.37)

EE, energy expenditure; EPQ-S, Endometriosis Patient Questionnaire; NHS-II PA, Nurses' Health Study II Weekly Physical Activity; SF-36, 36-Item Short-Form Health Survey; VAS, Visual Analog Scale.

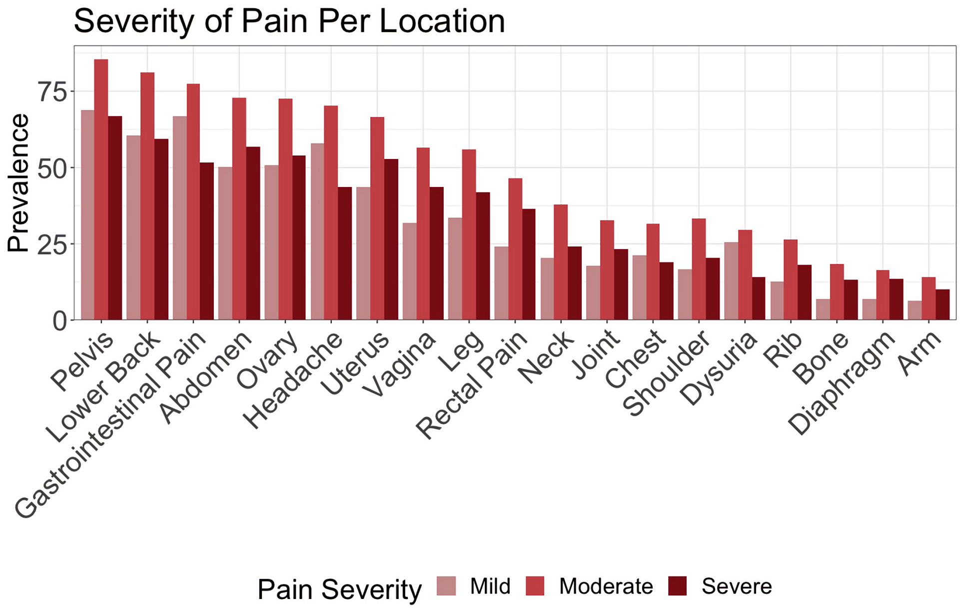

Figure 1 Prevalence of pain severity by location reported among participants (ie, unique counts of body area–severity per participant). Moderate intensity was the most frequently tracked across all body areas (14.1%–85.4%).

df=1438, p=0.661) (see online supplemental tables 2 and 3 for full results).

DISCUSSION

Summary of findings

We leveraged 90382 days of mHealth self-tracking data from 1009 women with endometriosis to investigate the association between exercise behaviour and day-level fluctuations in pain. For the average individual, the association between previous-day exercise and pain was moderated by their habitual exercise frequency, that is, the frequency with which they engaged in exercise in a typical week. This effect was consistent across participants and independent of person-level covariates. There was substantial between-person heterogeneity in day-level pain patterns. To our knowledge, this is the first study to quantify the association between day-level pain symptoms and exercise in an international sample of women with endometriosis and to identify habitual weekly exercise frequency as a moderator of this relationship.

Moderation effects

Previous-day exercise was associated with more favourable pain outcomes for participants who engaged in regular exercise at least three times per week in our sample. That is, these participants were more likely to report lower pain score and smaller increases (or larger decreases)

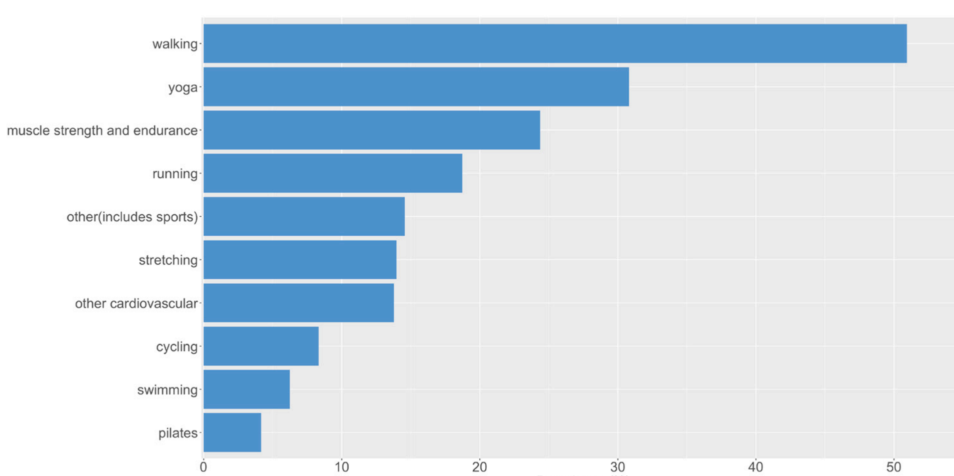

Figure 2 Prevalence of self-reported exercise modalities in the study sample. 'Other cardiovascular' category includes activities such as dancing, aerobics and using the elliptical machine. 'Muscle strength and endurance' category includes activities such as weightlifting and callisthenics. 'Other exercise' category includes sports activities such as skiing and soccer, multimodal exercises (eg, high-intensity interval training of both cardiovascular and muscular endurance) or those that did not fit into the other categories (eg, stabilising or balancing exercises, Wii fit or other home-based fitness activities).

Table 3 Results of the regression model estimating day-level total pain score (N=1009)

Conditional random effects	Variance (95% CI)		
Participant	1.09 (0.98 to 1.21)		
Conditional fixed effects	**Rate ratio (95% CI)**	**Log odds (SE)**	***z*-score**
Intercept	4.26*** (3.26 to 5.56)	1.45*** (0.13)	10.82
Menstrual status	1.29*** (1.25 to 1.32)	0.25*** (0.01)	20.31
Previous-day pain	1.02*** (1.02 to 1.03)	0.02*** (0.00)	29.69
Body mass index (BMI)	1.01* (1.00 to 1.02)	0.01 (0.00)	2.02
Mean weekly exercise frequency	0.93* (0.89 to 0.97)	−0.06** (0.02)	−2.96
Previous-day exercise	1.10* (1.05 to 1.15)	0.09**(0.15)	3.88
Some college education level	0.87 (0.83 to 1.56)	0.13 (0.15)	0.86
College or higher education level	0.93 (0.66 to 1.16)	−0.13 (0.14)	−0.92
Mean weekly exercise frequency×previous-day exercise	0.96** (0.95 to 0.98)	−0.03** (0.01)	−3.37
Zero inflation terms	**Rate ratio (95% CI)**	**Log odds (SE)**	***z*-score**
Intercept	0.17 (0.16 to 0.18)	−1.73***(0.02)	−62.96
Same-day exercise	5.34 (5.01 to 5.68)	1.67*** (0.03)	52.53

Previous-day pain and BMI were sample mean centred. BMI and education level were kept as covariates in the model based on their significant associations with mean day-level pain scores (Pearson's r=0.15 for BMI and Kruskal-Wallis χ^2=18.061 for education level, p<0.001).
*P<0.05, **p<0.001, ***p<0.0001.

in pain the day after an exercise bout, compared with not having exercised the previous day. In contrast, those who engaged in regular exercise less than twice a week were more likely to experience pain symptoms on days after having engaged in exercise. This is in line with the physical activity guidelines,[84 85] which recommend aerobic exercise at least three times per week and muscle-strengthening exercise at least twice per week.[86] However, there are no specific recommendations for endometriosis in the current guidelines; and systematic reviews recommend 'overall, general exercise' without further details due to the lack of adequate research on the optimal

Table 4 Results of the regression model estimating pain score difference (N=1009)

Conditional random effects	Variance (95% CI)		
Participant (intercept)	9.16 (8.28 to 10.13)		
Residual	26.83		
Conditional fixed effects	**B coefficient (SE)**	**95% CI**	***z*-score**
Intercept	2.70*** (0.51)	1.68 to 3.72	5.29
Menstrual status	1.47*** (0.09)	1.28 to 1.66	15.43
Previous-day pain	−0.86*** (0.01)	−0.87 to 0.85	−143.43
Body mass index (BMI)	0.05* (0.01)	0.01 to 0.10	2.86
Mean weekly exercise frequency	−0.27** (0.08)	−0.44 to 0.10	−3.12
Previous-day exercise	0.92** (0.18)	0.56 to 1.27	5.08
Some college education level	−0.84 (0.62)	−2.11 to 0.42	−1.35
College or higher education level	−2.07** (0.52)	−3.10 to 1.03	−3.96
Mean weekly exercise frequency×previous-day exercise	−0.14* (0.06)	−0.26 to 0.01	−2.22
Zero inflation terms	**B coefficient**	**95% CI**	***z*-score**
Intercept	−0.91*** (0.01)	−0.93 to 0.88	−63.84
Same-day exercise	0.70*** (0.02)	0.66 to 0.75	32.09

Previous day pain and BMI were sample mean centred. BMI and education level were kept as covariates in the model based on their significant associations with mean day-level pain scores (Pearson's r=0.15 for BMI and Kruskal-Wallis χ^2=18.061 for education level, p<0.001).
*P<0.05, **p<0.001, ***p<0.0001.

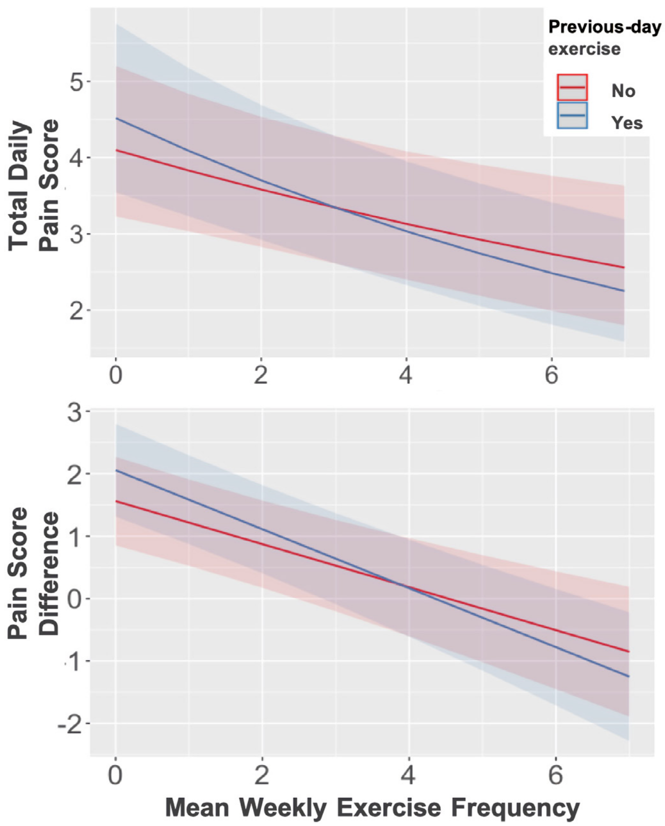

Figure 3 Moderation of effect of previous-day exercise by habitual exercise levels (x-axes). Y axes represent predicted day-level total scores (top) and differences (bottom) in pain. Shaded areas depict 95% CIs. At approximately three times/week of regular exercise, previous-day exercise starts to be associated with more favourable pain outcomes on the following day (ie, decrease from the model predicted mean scores), adjusted for other day-level and person-level factors.

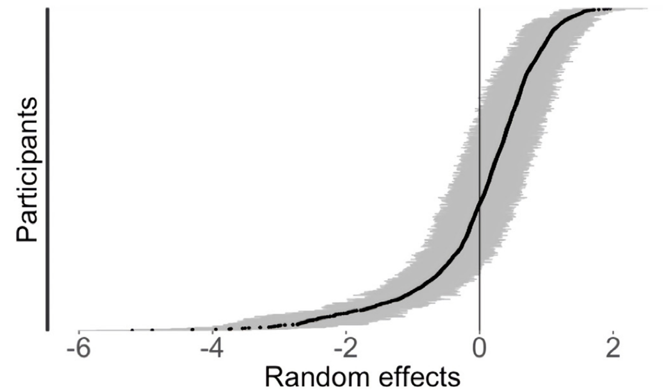

Figure 4 Plot of the random effect of the participant on total day pain scores estimated from the multilevel model (N=1009). Y-axis represents the range of estimated average pain scores for each participant. Each black dot represents one participant's mean (ie, random intercept), grey lines indicate 95% CIs. Distribution of points across the x-axis indicates large variability across individuals (ie, between-group variance), and the grey lines indicate the within-person variability in daily scores over time.

dose of exercise for endometriosis pain.[4 35] Our findings provide preliminary evidence for informing exercise recommendations for endometriosis pain management (ie, prevention or reduction), specifically for targeting those who are at greater risk of insufficient regular exercise due to acute exacerbation in their pain after exercise. This moderation effect suggests that an individual might need to develop a regular, sustained exercise behaviour (ie, habit) to start experiencing the favourable pain outcomes associated with acute bouts of exercise. Nevertheless, future experimental studies are warranted for a comprehensive investigation of this question.

Patterns of pain symptoms

Our findings of moderate pain in pelvis as the most frequently reported pain are in line with those from others on endometriosis[87] and various chronic pain conditions.[88 89] The distribution of the total daily pain scores was right skewed (ie, extreme scores on the higher ends of the range) with a mean score that was on the lower end of the range. This could partly be due to the data collection method which includes not just days where the participant experienced pain but also days without pain. Indeed, our participants on average did not report or experience any pain 6.25% of the time. In contrast, traditional study designs typically rely on recall of past pain experience aggregated over a period of time (eg, past week, month) and ask the participant to report their average or highest pain severity over this period.[90 91] Such recall-based techniques are prone to peak-and-end effects,[92] and catastrophising or other similar biases.[91 93] Recruitment from clinical referral points is a common practice and this has been attributed to higher normative scores in the literature,[90] as opposed to more even distributions of pain symptomatology among community-based samples.[94] Self-tracking facilitates documentation of not only severe pain, but also mild, moderate and no pain instances, therefore enabling a more realistic representation of the pain experience as it dynamically unfolds over time. This can reduce the likelihood of over-representing severe cases, which is a potential limitation attributed to data collected at point of contact in clinical settings.[17] However, it is difficult to make direct comparisons with other studies given the different pain measures, warranting further research.

Patterns of exercise behaviour

The mean weekly exercise frequency in the study sample was 1.43/week (SD=1.57, IQR=2.29), with only 24.5% (N=202) engaging in exercise at least three times a week. This suggests that individuals with endometriosis might be at increased risk of physical inactivity,[84 86] which is a risk factor for various comorbidities[95] and further linked to exacerbation of chronic pain.[96 97] These collectively underscore the need to focus efforts on promoting regular exercise in women with endometriosis. Notably, yoga and stretching were reported collectively by almost half of the sample within Phendo. This could indicate that participants use these approaches for pain relief, in line with a previous study reporting efficacy of hatha yoga.[32] Nevertheless, participants overall tracked a wide range of exercise modalities across the intensity spectrum (eg, yoga vs running/cycling) as helpful for their symptoms, suggesting between-individual variability in response to a given exercise type or intensity. This can be targeted through individualised exercise prescriptions,[24 98] providing precedence for undertaking a precision approach for pain self-management in endometriosis. Various individualisation approaches (eg, adaptive treatment strategies,[99] micro-randomised trials,[100] just-in-time adaptive interventions[101]) have been investigated for intervening on health behaviours, including PA.[5 100] It would be opportune to implement a similar N-of-1 intervention approach for identifying person-specific optimal 'dose' of exercise based on its parameters to target endometriosis pain symptoms.

Consideration of person-level factors

Another novel finding in our study was the similar point estimates for the effect of exercise on pain outcomes between those with clinician/surgical versus suspected diagnosis of endometriosis. Endometriosis is difficult to diagnose, with a 7.6-year delay between symptom onset and its surgical diagnosis.[18 102 103] Patients with endometriosis further face insurance-related challenges in accessing healthcare for their condition.[15 104] The participants without a formal diagnosis might have sought medical care for their symptoms but not received the needed care (eg, diagnostic testing, referral to a specialist), received false negative diagnostic tests results[102] or lacked adequate access to healthcare. This finding underscores the need for further research in endometriosis that considers self-report of endometriosis symptoms, instead of limiting to patients with a physician referral or relying on secondary data sources (eg, electronic health records).

Novel methodological contributions

In contrast to other existing questionnaires in the literature, the self-tracking items in Phendo measure momentary and daily pain symptoms and exercise—a time interval for which there are no standard validated, commonly used measures designed for frequent sampling. Phendo's pain tracking items are similar in design to other pain measures,[47 65] and have been indicated to be reflective of pain documentation in clinical records.[44] While mHealth studies have examined the validity, utility and specificity for various pain conditions[51 105 106] of their pain measurement approaches, a standard 'all-in-one' single outcome that captures the multidimensional pain experience across different populations remains to be established.[52 107] Computation of a composite pain has been proposed by others[108] as this circumvents numerous limitations in current pain assessment approaches, including lack of a standard single outcome that can be used universally,[107] or a validated instrument that captures all the constructs of persistent pain.[109] There is furthermore a lack of endometriosis-specific pain measures for repeated assessments, thus the heuristic composite pain measure allowed consideration of two dimensions of pain simultaneously in our analyses. The pain scores in the current study sample were moderately correlated with those from the Pelvic–Abdominal VAS and the SF-36 Bodily Pain measure, which were also similarly correlated with each other (r=0.46, p<0.0001). Nevertheless, future directions include evaluation of this measure in larger samples for its reliability and validity via a nomological network-based analysis.

Limitations

We acknowledge several limitations of this study, including reliance on self-reports for the type of endometriosis diagnosis and exercise behaviour. First, we used a binary measure of exercise in our analyses and did not have sufficient details on duration or intensity for inclusion in the analyses as potential moderators. Of note, similar mHealth measures of daily PA and exercise have been used by others[110–112] who reported concordance with accelerometer-based measures,[113] and higher correlations than self-report methods with accelerometer measures.[110 111] While we provide preliminary evidence toward the validity of Phendo's exercise tracking item both as a day-level and habitual measure,[57] future studies are needed to evaluate it in larger samples and compare against research-grade accelerometers. Similarly, we did not have granular daily data on pain medication use, as it was not investigated as a potential covariate in the analyses. In addition to medications, future studies could consider other pain management approaches for comparison with exercise, given previous research suggesting patients with endometriosis report using a variety of symptom management techniques.[44] Next, our sample consisted primarily of white, non-Hispanic women who are relatively consistent mHealth technology users and furthermore can understand English to use the app. Therefore, the results might differ among other groups including non-English speakers or those without an interest in mHealth use for self-management or monitoring.

Conclusion

In this study, we provide evidence that habitual exercise frequency is a potential moderator of the association between pain symptoms and previous-day exercise in endometriosis, indicating that those who regularly exercise at least ~3 times per week are less likely to report pain symptoms after having exercised on the previous day. Individuals with endometriosis are significantly more likely to have higher all-cause healthcare utilisation and direct healthcare costs than those without endometriosis, including twice the prevalence of opioid prescriptions for pain management[22] and prolonged duration of prescriptions.[21] While guidelines recommend prescribing exercise for management of pain in clinical populations, endometriosis (or general chronic) pain-specific recommendations to guide patients and providers on measurable parameters (time, type, intensity and frequency) are lacking. Future studies are warranted investigating the effects of both acute and chronic exercises on endometriosis pain with a focus on various types, intensities and duration.

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Contributors IE conceptualised the study, conducted the data analyses, prepared the first draft of the manuscript, and is responsible for the overall content as guarantor. SL-G and ENH were responsible for data acquisition, curation and management. NE acquired the funding and provided the mHealth infrastructure for the study (Phendo app). NE and SB provided guidance on the study design and data analyses. SB provided guidance on the copyediting of the manuscript. SB, NE, SL-G and ENH reviewed and provided feedback on the manuscript.

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Patient consent for publication Not required.

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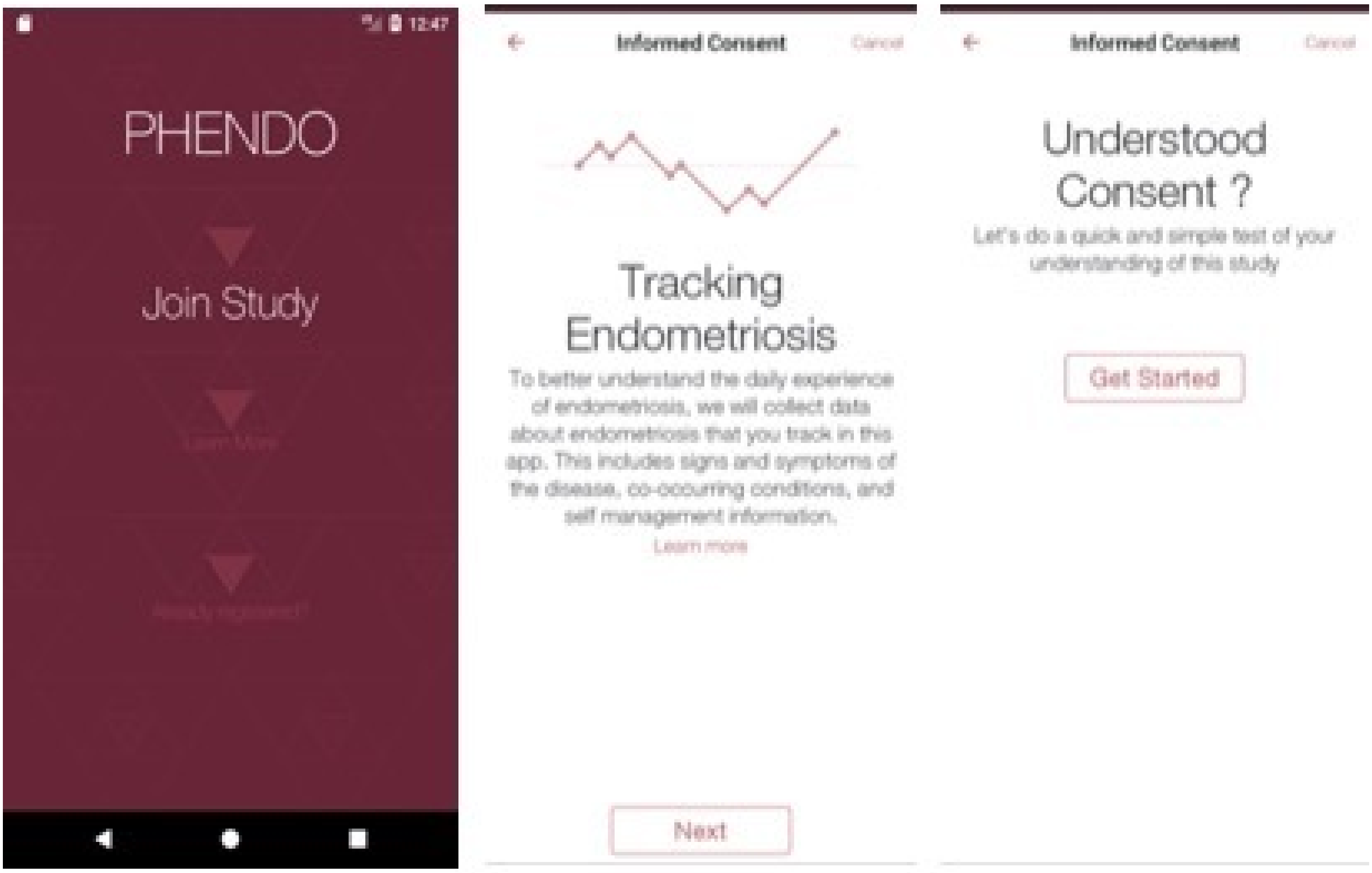
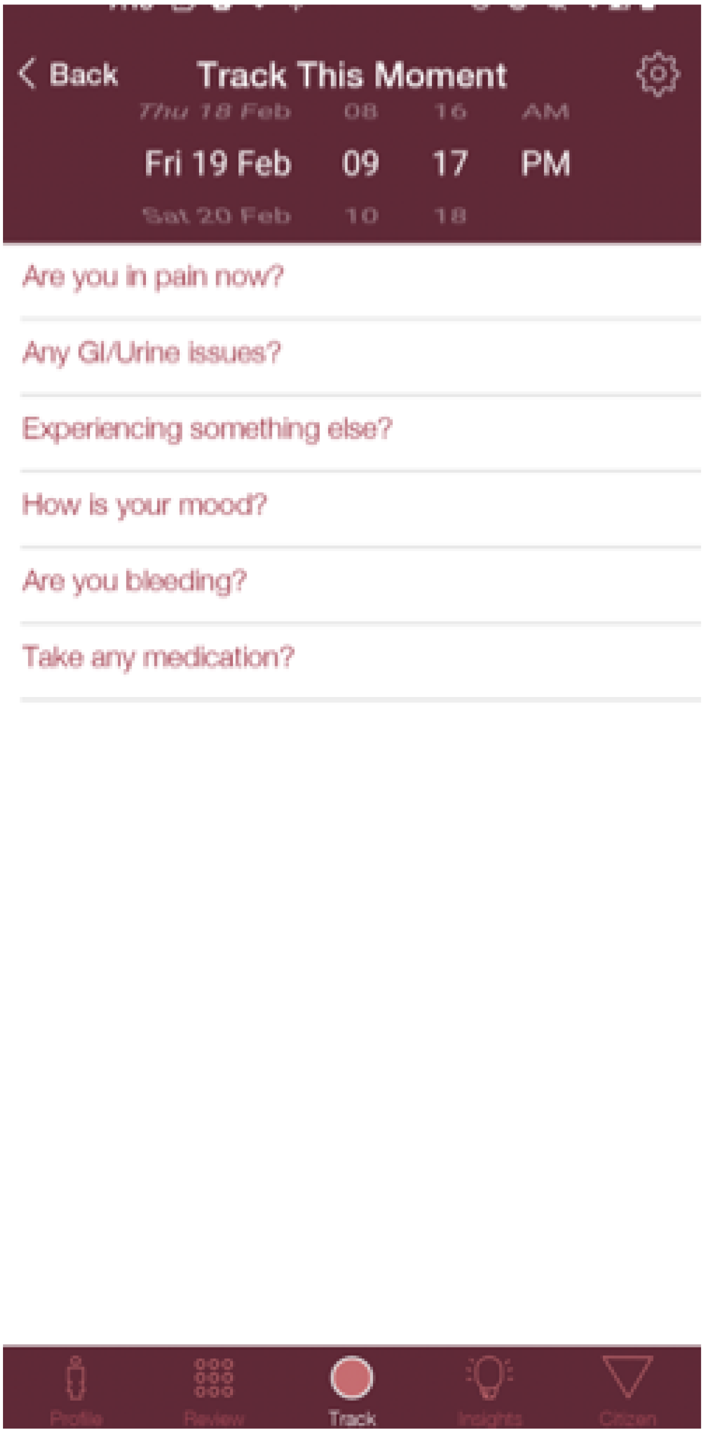

12:47
PHENDO
Join Study
Informed Consent
Tracking Endometriosis
To better understand the daily experience of endometriosis, we will collect data about endometriosis that you track in this app. This includes signs and symptoms of the disease, co-occurring conditions, and self management information.
Learn more
Next
Informed Consent
Understood Consent ?
Let's do a quick and simple test of your understanding of this study
Get Started


Back
Track This Moment
Thu 18 Feb 08 16 AM
Fri 19 Feb 09 17 PM
Sat 20 Feb 10 18
Are you in pain now?
Any GI/Urine issues?
Experiencing something else?
How is your mood?
Are you bleeding?
Take any medication?
Track


Cancel
What's happening in your gastrointestinal/urinary system?
Bs
Blood in stool
Uf
Frequent Urination
Cp
Can't Urinate
Up
Painful Urination
How severe is the symptom?
Mi
Mild
Mo
Moderate
Se
Severe
Done

Supplementary File 1. Missing Data Imputations.

Phendo is an observational research app and participants do not receive prompts from the research team to track any given item at a certain time. They are free to track (or not track) any given item as they wish. Consequently, missingness in the data occurs due to a variety of possible reasons that are not always known or easy to distinguish. For example, a period not tracked for a day could mean that the participant did not have a period, or they chose not to track, or did not use the app at all that day. To circumvent this issue, we took several measures. First, we limited data to days for which the participant tracked their pain, exercise and menstrual status at least once, as a proxy for app use. Next, we assigned a score of zero for pain on days where the participant had tracked exercise or menstrual status but not pain. This approach is motivated by 2 reasons. First, the nature of the pain question in Phendo (i.e., "Where is the pain?", "How severe is the pain?") assumes the participants to track when they feel pain and therefore a "No Pain" response is neither available in the app nor would make sense. Second, multiple imputation methods impute such that the resulting imputations are limited to the observed values and distributions. Thus by default it would omit the possibility of a zero in the resultant pain score distribution, which increases risk of overestimation of the scores in the sample.

BMI (calculated from participant reported height and weight) and education level were missing for 22% and 19% of the participants, respectively, and menstrual status was missing (i.e., not tracked) 22% of the time in the dataset. We imputed these 3 variables using multivariate imputations by chained equations [1] according to the heteroscedastic linear two-level structure of the data (i.e., hierarchical where, participant is the clustering variable) following standard multilevel multiple imputation methods. [1-4] We used two-level predictive mean matching for BMI and education level, which is a semi-parametric imputation method that limits imputations to the observed values and can preserve non-linear relations in the observed data, therefore the imputations do not deviate from the observed distribution[5] and two-level logistic regression for imputing menstrual status, using the rest of the dataset as the predictors. As per published recommendations,[1, 2] we also included the raw pain variable (i.e., with the missing values) as a predictor, to account for the possibility of an association between the missingness pattern of pain to these imputed variables. To assess the plausibility of the imputations and any significant deviance from the structure of the raw, non-imputed data, we inspected the imputation convergence plots, distributions of the imputed variables which are provided in Supplementary Figures 3 and 4.

Model specification. We used a zero-inflated negative binomial (ZINB) distribution when modeling the total pain outcome, as it has been demonstrated to provide the best fit for outcomes with over-dispersion and zero-inflation.[6-8] ZINB models consider two sources of zero observations: "sampling zeros" that are part of the underlying sampling distribution (i.e., negative binomial) and "structural zeros" that cannot score anything other than zero (i.e., participant did not track).[6] This virtue of the ZINB models allows for specification of the imputed zeros and prevents the risk of over-estimating effects and generates more conservative estimates for predictors of interest by estimating a separate zero-inflation term, as well as conditional model.[6] We specified the zero-inflation term such that it was dependent on the exercise variable for the day, in addition to specifying an overall general zero-inflation structure in the outcome through inclusion of an intercept, based on recommendations. [8] Menstrual status was not a significant predictor of zero-inflation and therefore removed from the zero-inflation term during the modeling process. We included participants who had at least 11 pairs of consecutive days of data in the final analytic sample as this provided sufficient amount of data to

1) ensure model convergence and improve reliability and accuracy of the estimates, particularly the random effects and their variances[9-12], and 2) adequately infer participants' habitual weekly exercise frequency by considering at least three weeks' worth of tracking to compute the weekly exercise frequency.

Ensari I, *et al. BMJ Open* 2022; 12:e059280. doi: 10.1136/bmjopen-2021-059280

Supplementary File 2. Imputation Model diagnostics.

Appropriateness and plausibility of the estimates from imputed models were inspected following published guidelines. First, we used measures of missing data information to assess pooled estimate variances. The fraction of missing information (λ) is interpreted as the proportion of variation in the parameter of interest due to the missing data. The relative increase in variance due to nonresponse (r) is interpreted as the proportional increase in the sampling variance of the parameter of interest that is due to the missing data. Values of λ over 0.5 indicate that the influence of the imputation model on the results is larger than that of the complete-data model, suggesting potential problems in the imputations. Supplementary Table 1 provides results of these variance estimates, indicating satisfactory imputation and model fit.

Supplementary Table 1. Measures of Missing data information

	Total Pain Score		**Difference in Pain**	
Conditional Fixed Effects	**λ**	***r***	**λ**	***r***
Intercept	0.21	0.27	0.23	0.31
Menstrual Status	0.13	0.15	0.19	0.23
Previous Day Pain	0.01	0.01	0.00	0.00
Body Mass Index	0.13	0.15	0.23	0.31
Mean Weekly Exercise Frequency	0.00	0.00	0.01	0.01
Previous Day exercise	0.01	0.01	0.00	0.00
Some College Education Level	0.26	0.36	0.35	0.55
College or Higher Education Level	0.23	0.31	0.21	0.28
Mean Weekly Exercise Frequency * Previous Day exercise	0.00	0.00	0.00	0.00
Zero Inflation Terms				
Intercept	0.00	0.00	0.00	0.00
Same Day Exercise	0.00	0.00	0.00	0.00

Next, we inspected propensity scores, which is a more recent and increasingly accepted method for inspecting the suitability of data imputation.[2, 13, 14] The goal is to compare the distributions of observed and imputed data conditional on the missingness probability. Under the missing at random (MAR) assumption, the conditional distributions of the observed and missing data should be similar if the assumed model for creating multiple imputations has a good fit. To do this, we first estimate the probability of each record being incomplete (i.e., “response propensity”) in the presence of missing data by conditioning on the response indicators as well as the observed covariates. The probabilities are then averaged over the imputed datasets to obtain stability. Supplementary Figure 3 plots BMI, education category and menstrual status against the propensity score in each dataset. The distributions of the blue and red points are match up well without significant discrepancies (e.g., mismatch in patterns, imputed data systematically shifted toward one side of the axis).

Supplementary Table 2. Post-hoc analyses with endometriosis diagnosis included as a covariate. Conditional model results of the negative binomial model estimation of day-level total pain score (N=608).

Random Effects	**Variance (95% CI)**
Participant (Intercept)	1.10 (0.99, 1.22)

Fixed Effects	**Log Odds (SE)**	**z-score**
Intercept	1.37*** (0.12)	10.97
Menstrual Status	0.25*** (0.01)	21.40
Previous day Pain	0.02*** (0.01)	21.40
Body Mass Index	0.01* (0.004)	2.81
Mean weekly Exercise Frequency	-0.06** (0.02)	-3.01
Previous day exercise	0.09** (0.02)	3.85
Clinician diagnosis of endometriosis	-0.07 (0.10)	0.01
Self-diagnosis of endometriosis	-0.11 (0.11)	-1.01
Some college education level	0.22 (0.13)	-1.63
College or higher education level	-0.01 (0.12)	-0.12
Mean weekly Exercise Frequency*Previous day exercise	-0.03*** (0.01)	-3.42

SE=Standard Error. *p=0.001, ** p <0.001, ***p<0.0001. B coefficients are rate ratios. BMI =Body Mass Index. BMI and previous day pain were group mean centered.

Supplementary Table 3. Post-hoc analyses with endometriosis diagnosis included as a covariate. Conditional model results of the regression model estimation of pain score difference (N=1009).

Conditional Random Effects	**Variance (95% CI)**
Participant (Intercept)	13.34 (12.09, 14.93)

Fixed Effects	**B coefficient (SE)**	**z-score**
Intercept	2.45*** (0.46)	5.22
Menstrual status	1.46*** (0.08)	16.98
Previous day pain	-0.86*** (0.01)	-144.11
Body mass index	0.07* (0.01)	4.47
Mean weekly exercise frequency	-0.27** (0.09)	-3.03
Previous day exercise	0.92*** (0.18)	5.13
Clinician diagnosis of endometriosis	-0.05 (0.32)	-0.16
Self-diagnosis of endometriosis	-0.45 (0.43)	-1.29
Some college education level	-0.30 (0.51)	-0.58
College or higher education level	-1.72** (0.47)	-3.67
Mean weekly exercise frequency*Previous day exercise	-0.14* (0.06)	-2.31

SE=Standard Error. *p<0.05, ** p <0.01, ***p<0.0001. Body Mass Index and previous day pain were group mean centered.

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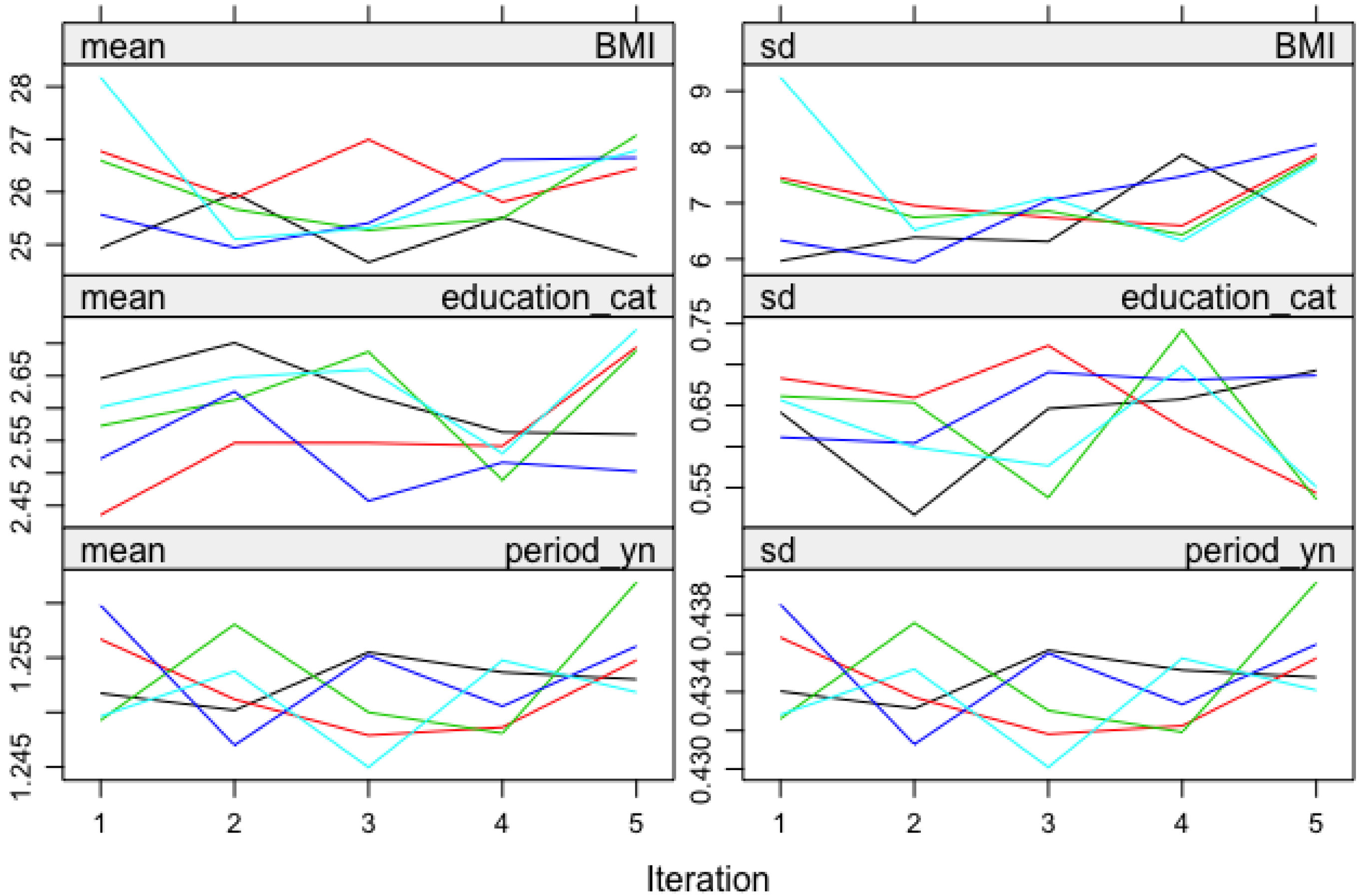
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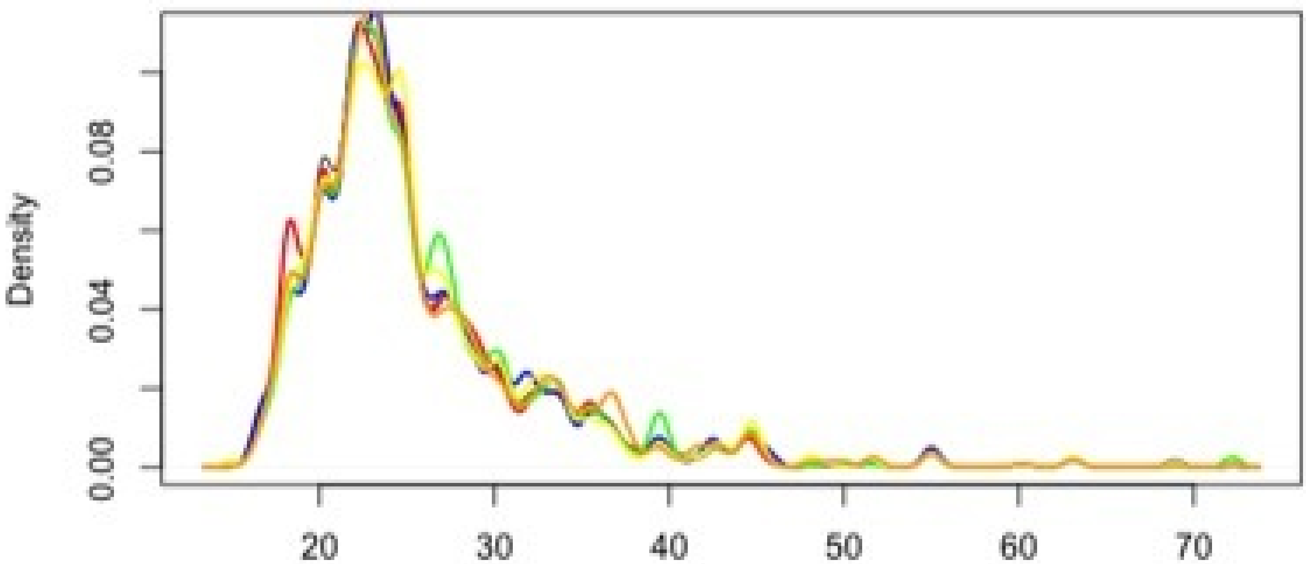
Iteration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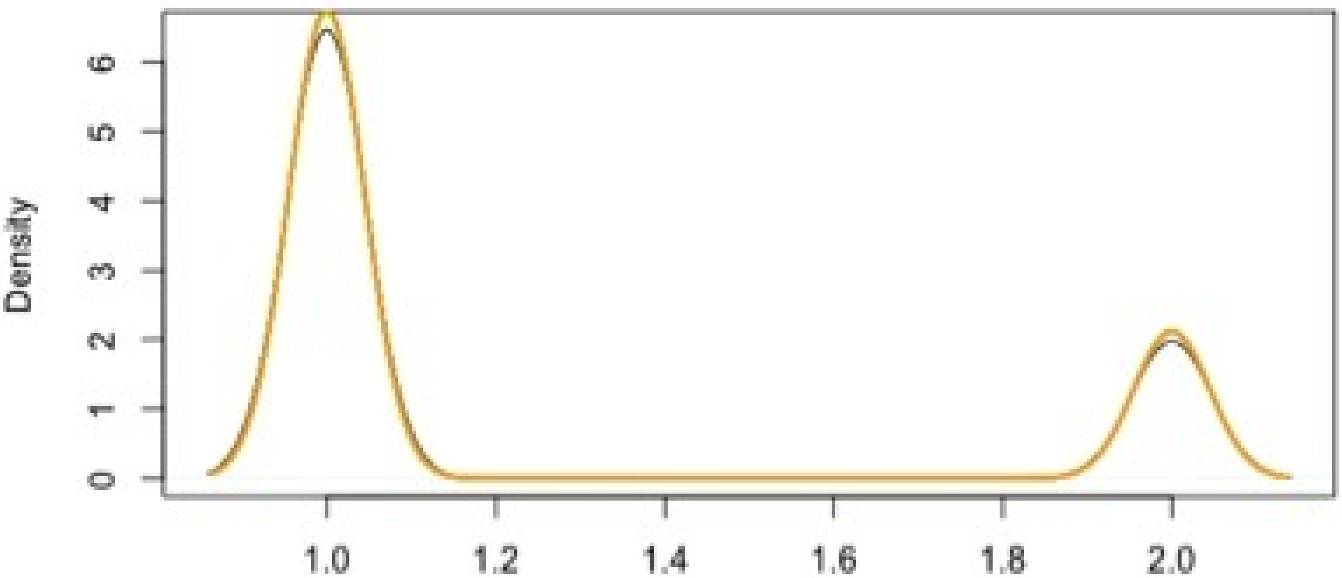
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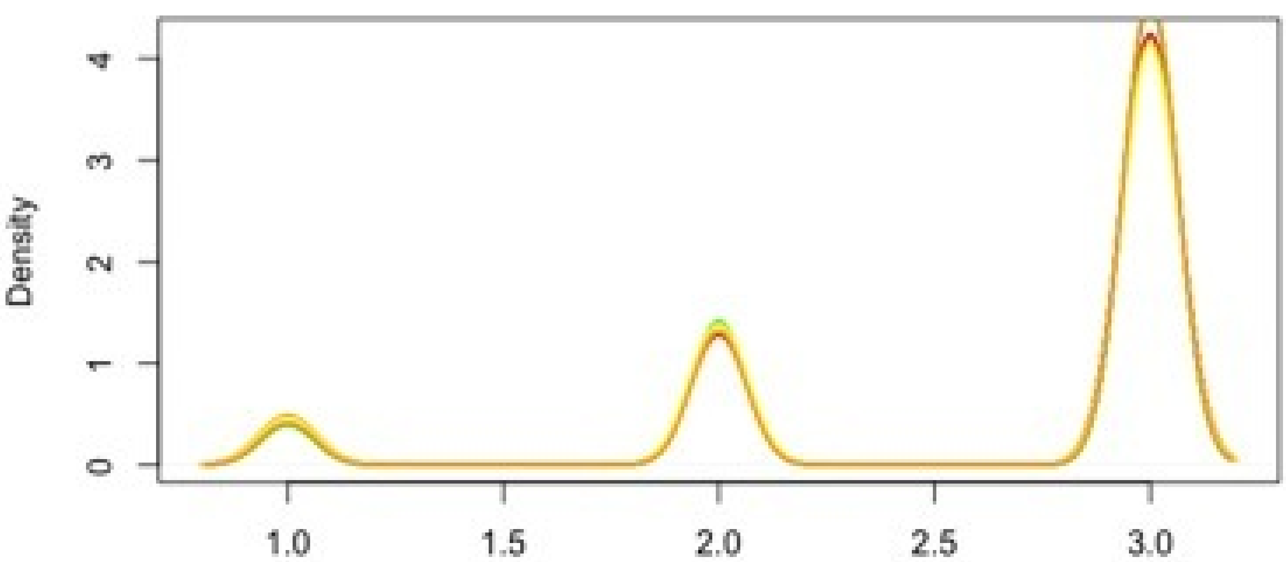
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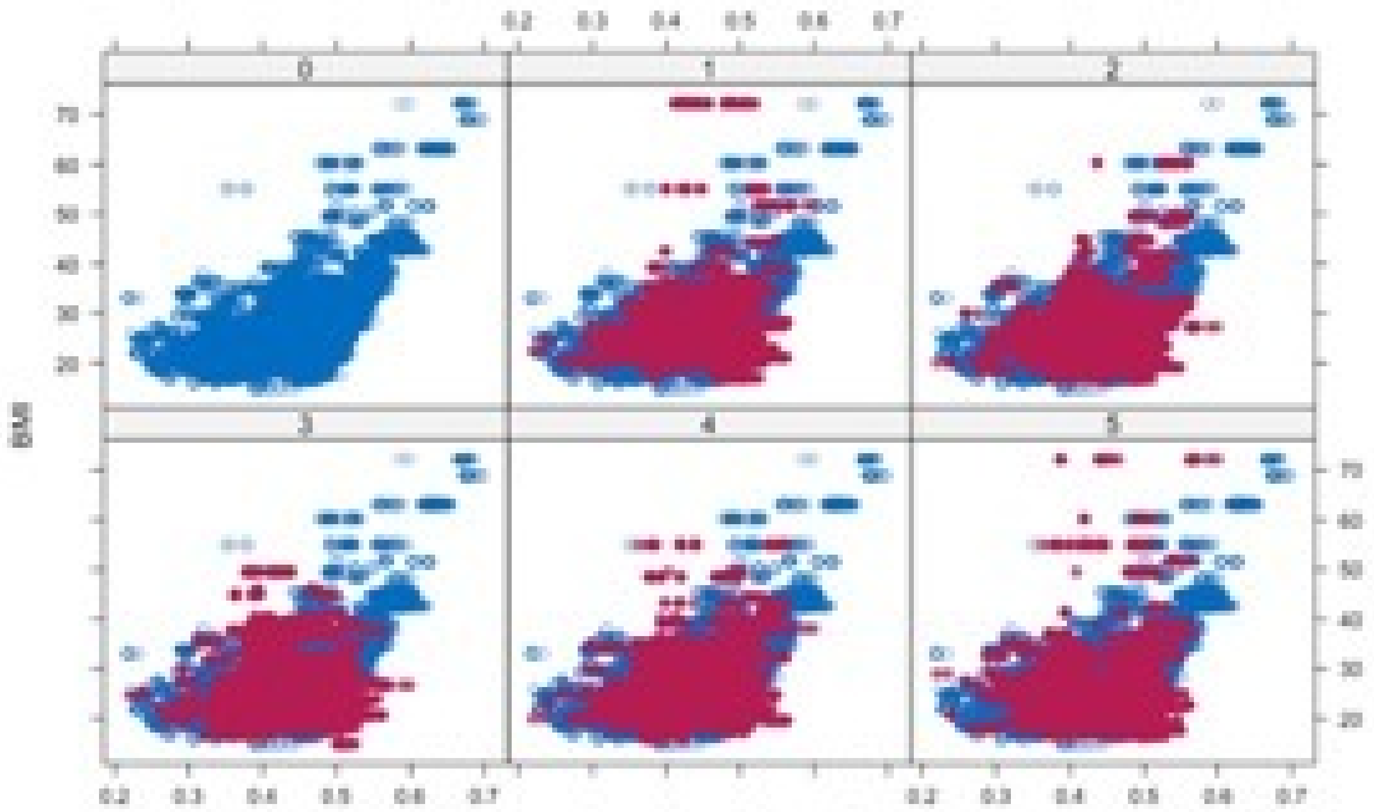
2.5
3.0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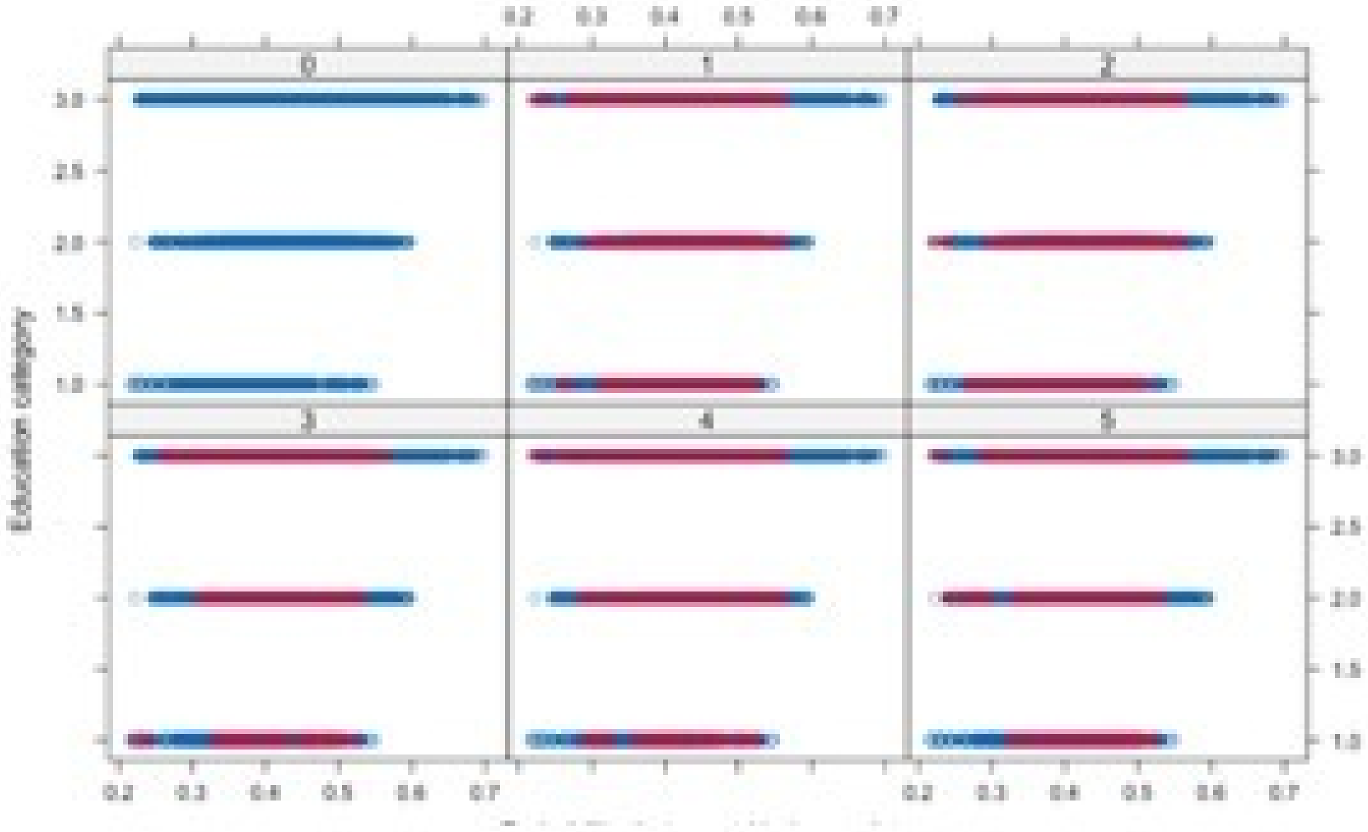
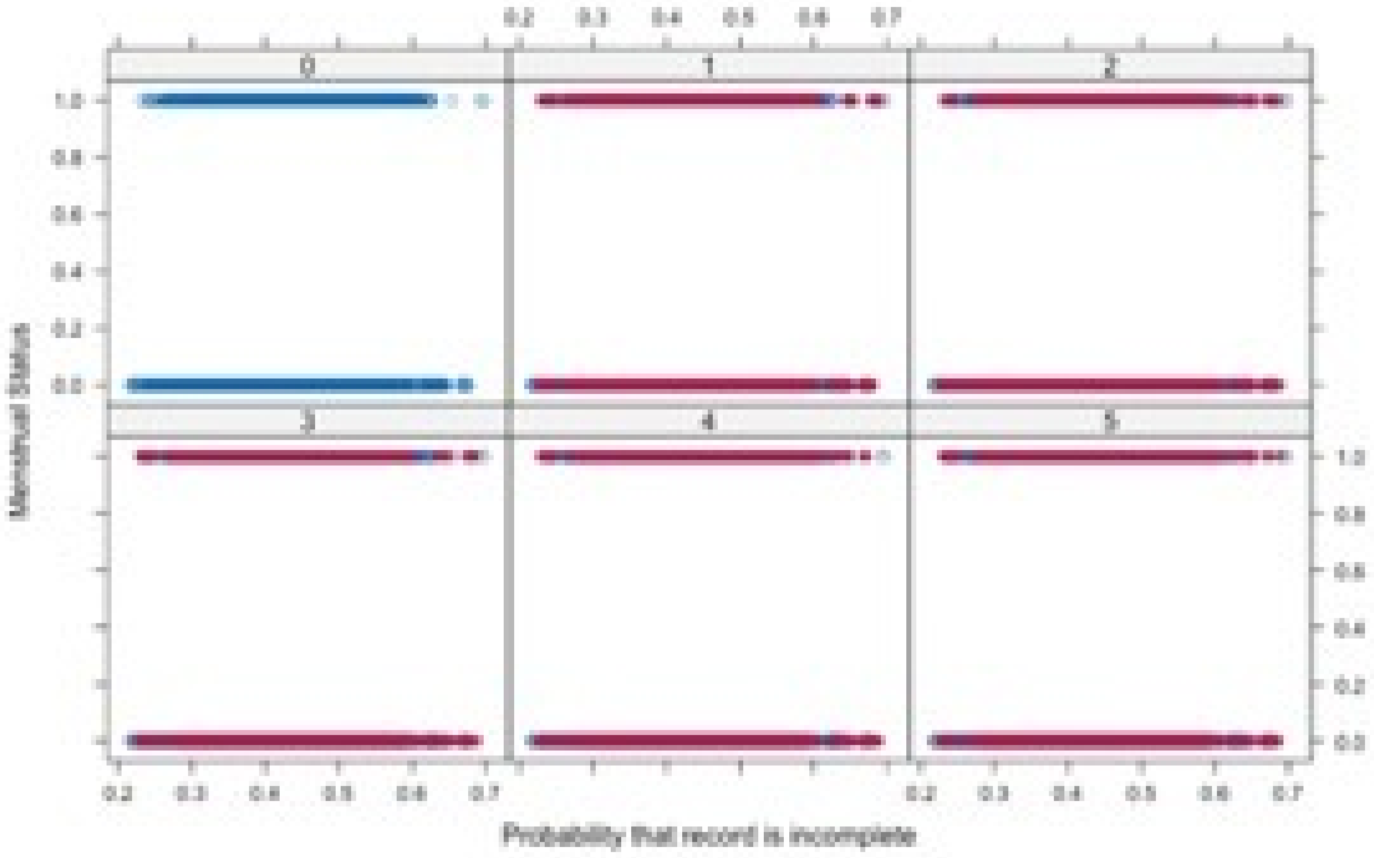

Education category


Menstrual Status
Probability that record is incomplete