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Changes in Exhaled Carbon Dioxide during the Menstrual Cycle and Menopause

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Keywords
Menstrual cycle · Menopause · Lumen · CO_2 · Ovulation

Abstract
Introduction: The menstrual cycle (MC) reflects multifaceted hormonal changes influencing women's metabolism, making it a key aspect of women's health. Changes in hormonal levels throughout the MC have been demonstrated to influence various physiological parameters, including exhaled carbon dioxide (CO_2). Lumen is a small handheld device that measures metabolic fuel usage via exhaled CO_2. This study leverages exhaled CO_2 patterns measured by the Lumen device to elucidate metabolic variations during the MC, which may hold significance for fertility management. Additionally, CO_2 changes are explored in menopausal women with and without hormonal replacement therapy (HRT). ***Methods:*** This retrospective cohort study analyzed exhaled CO_2 data from 3,981 Lumen users, including eumenorrheal women and menopausal women with and without HRT. Linear mixed models assessed both CO_2 changes of eumenorrheal women during the MC phases and compared between menopausal women with or without HRT. ***Results:*** Eumenorrheic women displayed cyclical CO_2 patterns during the MC, characterized by elevated levels during the menstrual, estrogenic and ovulation phases and decreased levels during post-ovulation and pre-menstrual phases. Notably, despite variations in cycle length affecting the timing of maximum and minimum CO_2 levels within a cycle, the overall pattern remained consistent. Furthermore, CO_2 levels in menopausal women without HRT differed significantly from those with HRT, which showed lower levels. ***Conclusion:*** This study reveals distinct CO_2 patterns across MC phases, providing insights into hormonal influences on metabolic activity. Menopausal women exhibit altered CO_2 profiles in relation to the use or absence of HRT. CO_2 monitoring emerges as a potential tool for tracking the MC and understanding metabolic changes during menopause.

Introduction

The menstrual cycle (MC) is a complex physiological process regulated by several sex hormones, and changes in these hormones have been found to affect women's metabolism [1, 2]. The detection of metabolic related alterations in relation to the MC was previously demonstrated by exhaled volatile organic compounds [3], arterial carbon dioxide (CO_2) pressure [4], and end-tidal CO_2 pressure (etpCO_2) [5]. CO_2 is a fundamental marker of metabolic activity in the human body and provides valuable insights into physiological processes [6]. Understanding the patterns of CO_2 levels in different female populations can shed light on the physiological changes

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associated with hormonal status and provide valuable information for women's health and overall metabolic health. Furthermore, such CO_2 patterns might be used for tracking the MC and the fertile window.

There are various methods for tracking the MC [7, 8], among which are basal body temperature tracking, which involves measuring a woman's body temperature at rest each morning [9–11]; vaginal discharge tracking, which requires daily follow-ups of the consistency and amount of cervical mucus throughout the cycle [7, 12]; and urinary hormone kits, that measure the LH surge that occurs just before ovulation [13, 14]. Methods such as these can be demanding since they might require precise protocol adherence and inability to comply with these can result in inaccuracies [15, 16]. Therefore, there is a need for improved and more precise methods to determine the timing and progression of the MC stages.

The transition into menopause, commonly manifested by menstrual irregularity and hormonal variability, is often characterized by major metabolic changes [17–20], and has been widely discussed elsewhere [21, 22]. Post-menopausal women no longer experience the progesterone surge during the luteal phase as eumenorrheic women [22], and during menopause, hormone replacement therapy (HRT) can influence progesterone levels [23, 24].

The Lumen device is a portable breath-analyzer that measures metabolic fuel utilization via exhaled CO_2 and was found to be in agreement with the respiratory exchange ratio measured by the metabolic cart [25]. This retrospective analysis examines exhaled CO_2 measurements collected by Lumen users, objective (i); to evaluate changes during the MC phases of eumenorrheic women and objective (ii); eveluate the differences in CO_2 measurements of two groups of menopausal women: with and without the use of HRT.

Methods

CO_2 Measurements

Exhaled CO_2 measurements were obtained using the Lumen device (Metaflow Ltd., Tel-Aviv, Israel) according to its breathing maneuver, with the Lumen app guiding the participant through each phase of the Lumen maneuver, as previously described [25]. To avoid the immediate effect of food consumption or workout on the measured CO_2, solely morning fasted state measurements were used for the analysis.

Participants and Inclusion Criteria

This analysis is based upon deidentified data collected from users of the Lumen device and app. All data were collected retrospectively between the 1st of October, 2022, and the 4th of October, 2023. Inclusion into analysis had to meet the following criteria:

1. Gender; female users only.
2. Age; all participants were at least 18 years of age.
3. Lumen-app usage duration (retention); a duration equivalent to three entire MCs (up to 105 days).
4. Lumen-app activity level (engagement); a minimum of 3 measurement days for each half-cycle for euomenorrheic women or 15 days for menopausal women.
5. For eumenorrheic cohort only; reported cycle length must range between 23 and 35 days.

Study Design and In-App Data Gathering

This is a retrospective cohort study comprising Lumen device and app users. During app onboarding, all users were requested to specify their gender (assigned at birth), date of birth, height, and weight. All female users were offered the option of entering their MC data, and those who chose to do so were required to submit their MC start date at the beginning of each cycle. For eumenorrheic users, this is used as the cycle start index day. For all other users, the start of index day is their first recorded measurement. Furthermore, they were asked to select their current method of hormonal birth control with a short list of possible hormonal contraceptive types. Alternatively, users going through menopause would indicate this at the beginning of their user journey and had to indicate whether they were using HRT (illustrated in Fig. 1).

The study population was divided into two main groups, in accordance with their self-reported personal information (Fig. 2). Notably, only 3.3% of the cohort responders identified themselves as using HBC, not providing a substantial population size and were therefore excluded from the analysis.

Accordingly, they were assigned to the fitting population group:

1. Eumenorrheal non-hormonal birth control (non-HBC) users: Indicated either no use of birth control or the use of a non-hormonal birth control method.
2. Menopausal women: Indicated either no use of hormonal therapy (noHRT) or the use of hormonal therapy (HRT).

Data Analysis and Statistics

Analyses were performed as follows:

- For objective i, Figure 3a: statistical analyses were conducted using Python (python 3.8.5; Project Jupyter). The evaluation of objective i was performed by fitting a linear mixed model (LMM). Morning fasted CO_2 was set as the outcome variable, MC phase was set as the main independent variable and age, BMI and the length of the cycle were set as covariates. UserID was defined as a random effect variable and the menstrual phase was selected as the reference group.
- For objective i, Figure 3b: The evaluation of the relative change in CO_2 between consecutive MC phases was performed by One-way ANOVA using GraphPad Prism 10.2.1 (GraphPad Software Inc.).
- For objective i, Figure 4a, b and d: the analysis was performed by R (version 4.3.1); CO_2 level of each cycle for each participant was normalized using the Z-score method. Smoothing spline estimator was used for Figure 4a and b. Additionally, for Figure 4b, the time scale was transformed to fit a relative scale ranging from 0 to 100%. This was done by calculating the relative length of a "cycle day" for each cycle of each participant. For the estimation of the cyclic similarity between each cycle length, Pearson cross-correlation was used

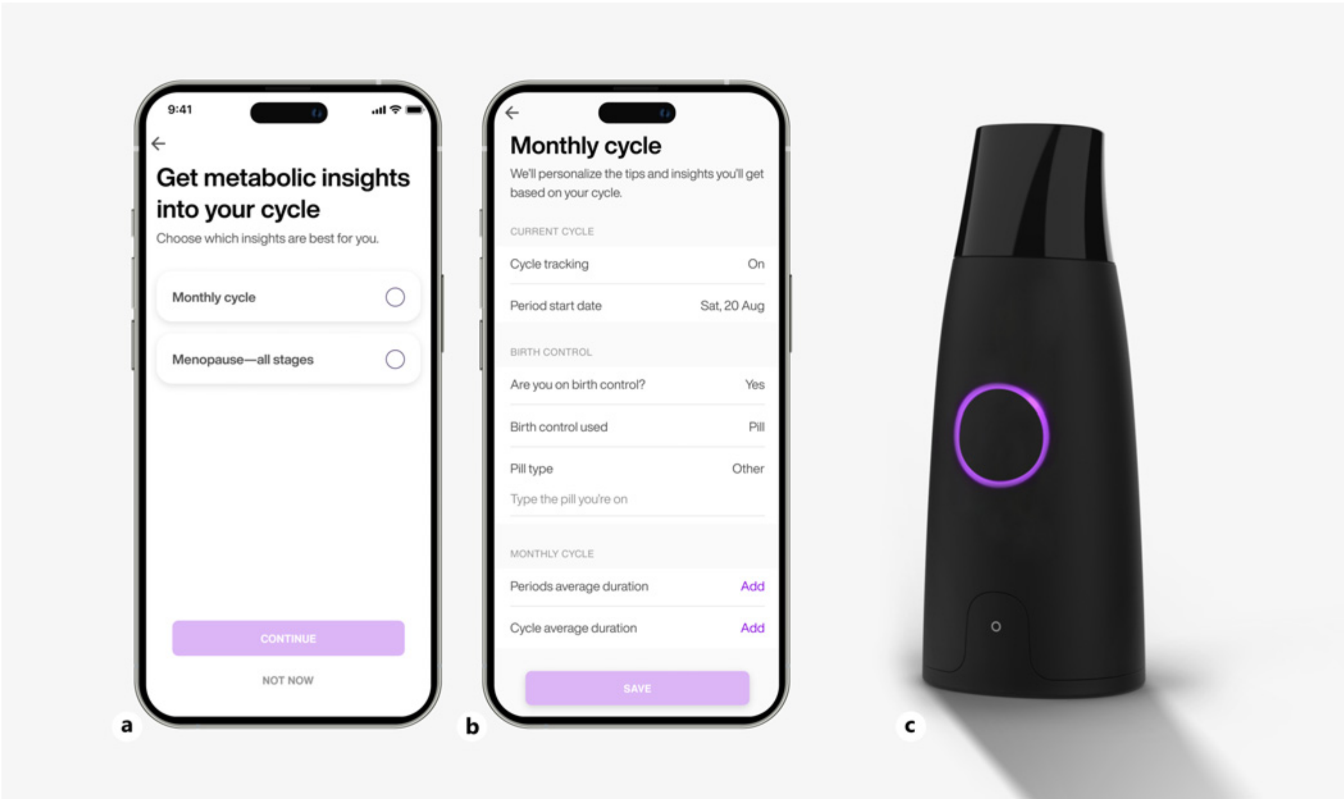

Fig. 1. Screenshot from the onboarding process of the Lumen app. All users provided their personal information regarding age, gender, height, and weight. Additionally, users were requested to specify whether they are menopausal or menstruating (**a**), and whether they are using HRT or HBC and indicate their MC start date (**b**). Illustration of the Lumen device (**c**).

to determine the optimal lag distance between each cycle length which yields the highest correlation, shown in Figure 4b and d.

- For objective ii, Figure 5: statistical analyses were conducted using Python. The evaluation was analyzed by LMM, CO_2 was set as the outcome variable while age and BMI as covariates. UserID was defined as a random effect variable.

Among all performed analyses, a p level of <0.05 was set for statistical significance.

Results

Participant Characteristics

A total of 3,981 participants were included in the analysis; non-HBC 1,191, noHRT 2,095, HRT 695 (Table 1 summarizes their characteristics). Female users were divided into groups according to their responses during the app-onboarding; eumenorrheic, menopausal women with or without hormonal replacement therapy (HRT or noHRT, respectively).

CO_2 Pattern during the MC of Eumenorrheic Women

A cyclical pattern of CO_2 levels can be observed in the data from three accumulated MCs of eumenorrheal women. Figure 3a present data from all cycle lengths, whilst exhibiting days 1–28 with the MC phase breakdown. For this analysis, we used the LMM prediction method, where CO_2 was set as the dependent variable while the main independent variable was the cycle phase. BMI, age, and length of the cycle were considered as covariates. UserID was set as a random effect variable. A statistically significant change in CO_2 levels was found between each MC phase, displaying an increase in CO_2 levels during the estrogenic and ovulation phases, compared to the first (menstrual) phase of the MC. Furthermore, a decrease in CO_2 levels was exhibited during post-ovulation and pre-menstrual phases compared with the menstruation phase (Table 2). While age and the length of the MC were not found to be significant predictors of CO_2 levels, BMI showed a significant positive association with CO_2 levels. Figure 3b

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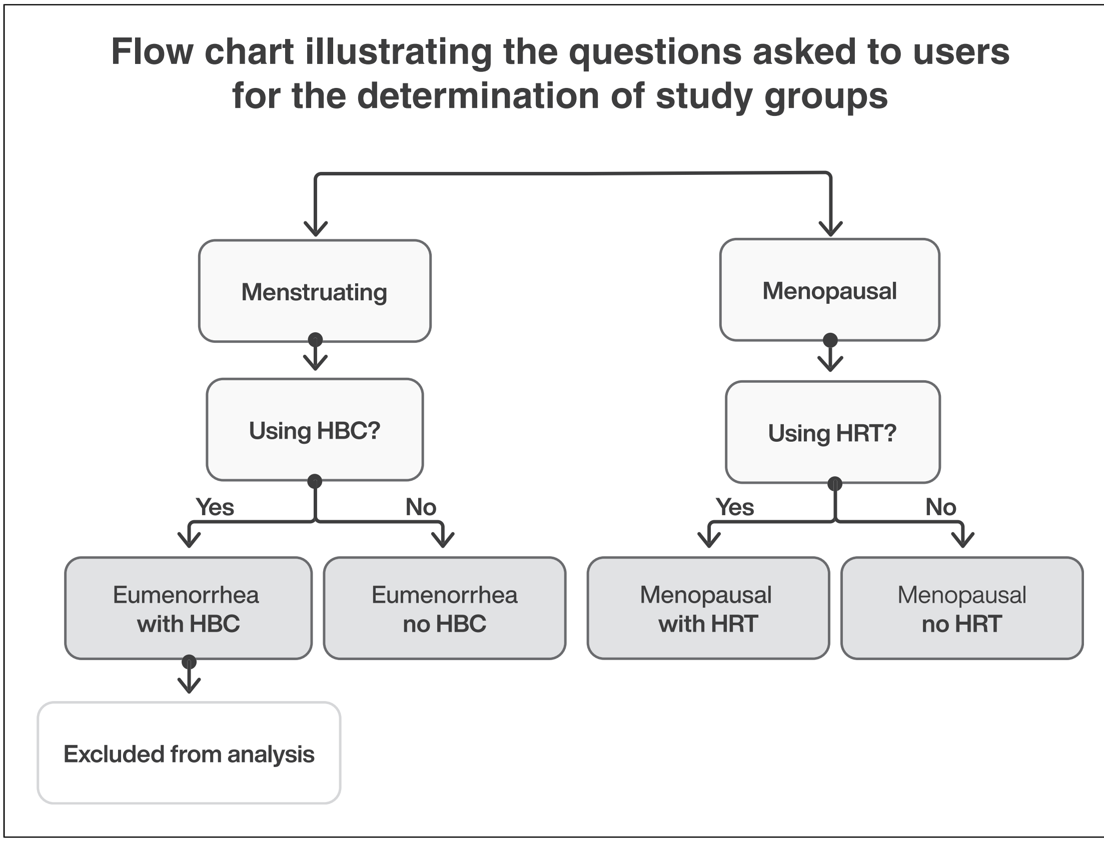

Fig. 2. Determination of study groups. All users were assorted into groups according to the personal information they provided during the app onboarding process. Number of Lumen users in each group is indicated.

depicts the relative change in CO_2 levels between consecutive MC phases. A one-way ANOVA was conducted to analyze these relative changes, finding a significant effect of MC phase on CO_2 levels ($F_{(4, 14,788)} = 319.4$, $p <$ 0.0001). Due to variations in cycle lengths, we grouped measurements based on the calculated duration between the starting days of consecutive MCs, to assess the composition of the general population's rhythmic cyclical pattern. Figure 4 displays that while the length of the cycle will influence the position of the maximum and minimum CO_2 levels (shown in Fig. 4a and c), the overall pattern is consistent for all cycle lengths, as exhibited by the high correlation between all cycle length groups (Fig. 4b and d).

Differences in CO_2 between Menopausal Women with or without HRT

Since there is a drastic shift in sex-hormone pattern during and following the transition into menopause [22], we conducted a comparison of the CO_2 changes within menopausal women (Fig. 5). For this analysis, we used LMM prediction method, where CO_2 was set as the dependent variable and the main independent variables were HRT, BMI, and age. Results showed a statistically significant higher CO_2 level in menopausal women not using HRT (noHRT group) compared to menopausal women using HRT (HRT group). Both age and BMI were positively associated with CO_2 levels (LMM, Table 3).

Discussion

The female MC is a dynamic physiological process influenced by an interplay of sex hormones, making it an important subject for women's health and metabolic research. In this study, we show that CO_2 levels measured daily throughout the MC of eumenorrheal women exhibit a cyclic pattern characterized by a significant increase in CO_2 levels during the estrogenic and ovulation phases, followed by a decline during the post-ovulation and pre-menstrual phases. This observed

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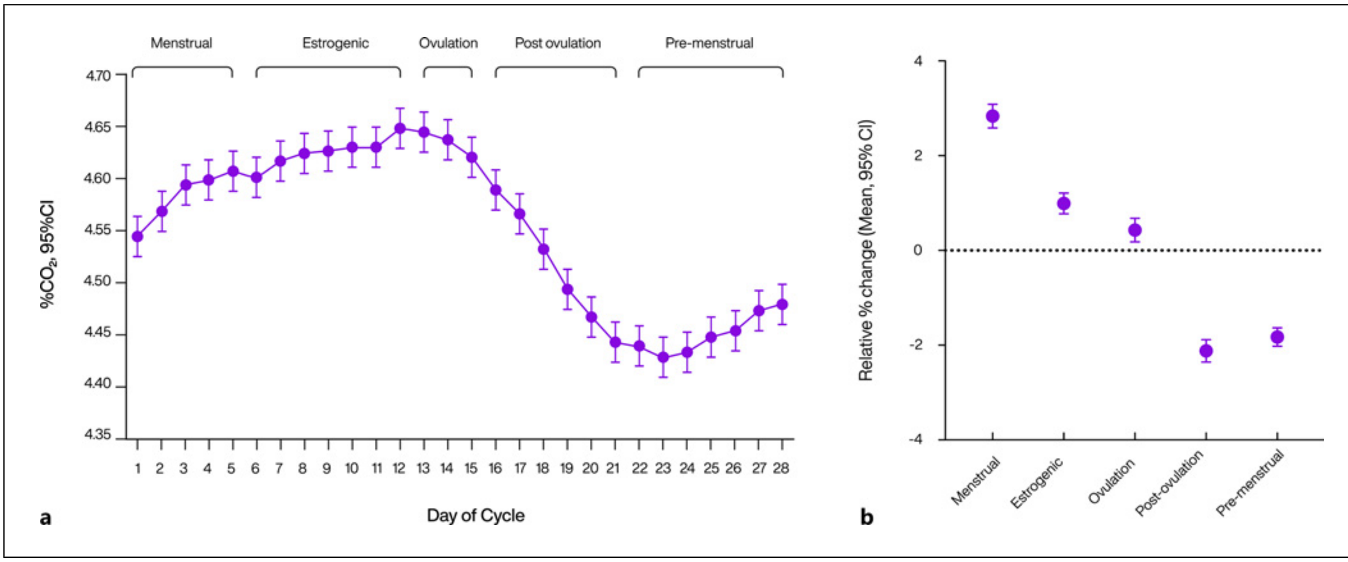

Fig. 3. CO_2 changes of eumenorrheic women during the different menstrual phases. **a** Accumulated data of multiple menses of all cycle lengths, drafted over a 28-day window. The different phases of the MC are presented at the top. **b** Relative CO_2 change between each following MC phase. Y axis exhibits % change between each following phases. Results of the menstrual phase are calculated in relation to the pre-menstrual phase.

pattern persisted despite variations in age and cycle length ranging from 23 to 35 days. Although BMI did not change within each participant throughout the study, BMI was positively associated with the level of CO_2. No effect of age and the length of the cycle over CO_2 levels were found. Our findings show different CO_2 levels for menopausal women not using HRT compared with menopausal women who indicated using HRT, which exhibited significantly lower CO_2 levels.

Understanding the timing and progression of different stages within the MC is crucial for various aspects of women's health and reproductive physiology [26]. Accurate identification and tracking of these stages are essential for fertility management and the diagnosis and treatment of menstrual disorders.

Amongst sex hormones regulating the cyclicity of the MC is progesterone, which, during the second half of the cycle, reaches its peak in the luteal phase, and during the pre-menstrual phase, its levels drop to baseline [1]. Hadziomerović and Moeller et al. [5, 27] have previously described how the administration of exogenic progesterone results in an immediate reduction of $etpCO_2$, thus showing the impact of progesterone on CO_2. This corresponds to previously observed changes in CO_2 during the MC, exhibiting decreasing CO_2 levels occurring while progesterone levels are elevated [28, 29].

While not directly assessed in this study, our results suggest that if progesterone increased as anticipated during the post-ovulation and pre-menstrual phases, there was a corresponding decline in CO_2 levels, aligning with prior research [27–30]. Menopausal women undergo hormonal changes, such as decreased progesterone levels. Our findings of higher CO_2 levels for menopausal noHRT women, compared to those with HRT, suggest an association with progesterone changes. This underscores the need for further research to investigate the potential implications of progesterone fluctuations in CO_2, both for eumenorrheal and menopausal women.

This study does hold some notable limitations. As this is a retrospective real-world study based upon historical user-provided information, it might be prone to recall bias and affected by possible inaccuracies. This might lead to group misclassification, introduce random errors, or reduce the precision of estimates. Consequently, it could potentially mask true associations between variables. In order to minimize such bias, data quality-controlled measures such as data cleaning, duplicate and outlier detection and the identification of inaccuracies or discrepancies were made. Furthermore, the reliance upon user-generated data can affect variability since the start date of the MC and its regularity are subject to individual interpretation, and inaccuracies in reporting MC-related details may influence the precision of the observed results. The absence of direct

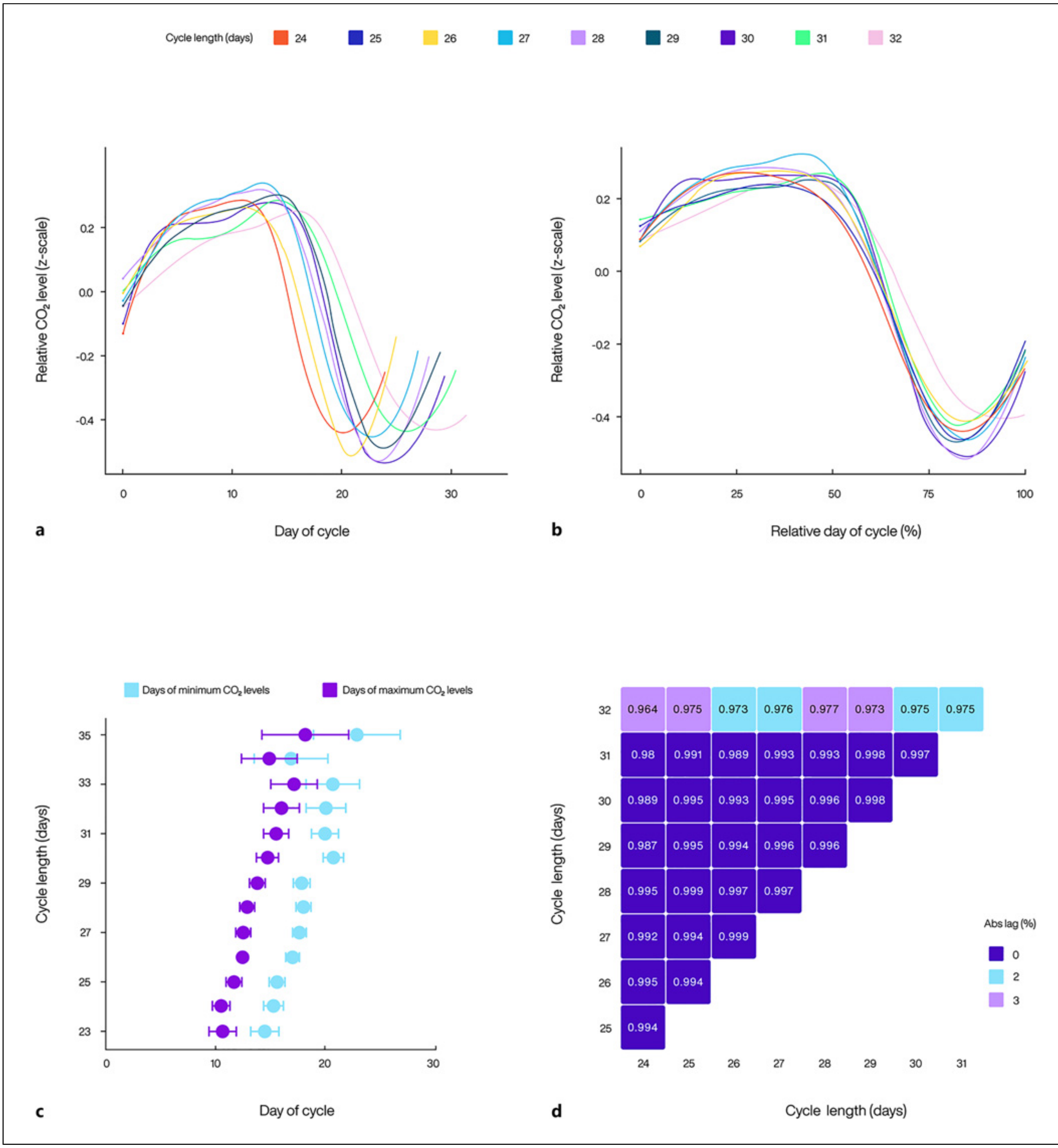

Fig. 4. CO_2 changes of different MC lengths. Cycle lengths were determined according to the calculated duration between each menstruation starting day, of two following cycles. **a** Time is displayed on a day of cycle scale, as reported by the participants. **b** Relative time-scale in percentages, calculated for each cycle length of each participant, indicating the overall pattern is consistent for all cycle lengths. **c** Cycle length characteristics; the length of the cycle will influence the position of the maximum and minimum CO_2 levels. **d** Pearson cross-correlation matrix grouped according to cycle length. Color indicates the necessary number of lags for achieving optimal correlation rate.

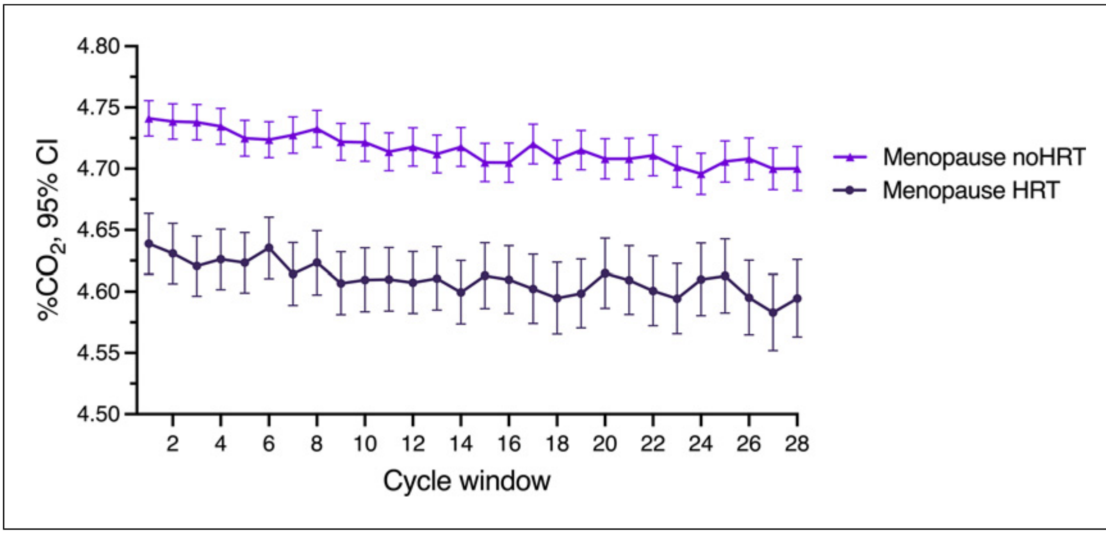

Fig. 5. Averaged daily CO_2 measurements of the two menopausal groups. Data drafted over a 28-day moving window of accumulated measurements per day.

Table 1. Summary of the participants physiological and user-app characteristics

	Eumenorrhea	Menopause noHRT	Menopause HRT
Number of users, *n*	1,191	2,095	695
Age, years	41.0±5.5	55.55±8.2	55.34±7.1
BMI, kg/m^2	27.47±5.6	29.16±6.2	26.92±4.9
Body weight, kg	75.49±16.9	79.7±17.9	73.79±15
Cycle length, days	27.73±1.9	n/a	n/a
Total number of measurements, *n*	63,541	121,419	39,305
Average number of measurements per user, *n*	53.35±20.8	57.95±21.9	56.55±21.1

Data shown as mean ± SD.

Table 2. Determinants of CO_2 changes along the different phases of the MC

Phase/parameter	β (95% CI)	*z* statistics	*p* value
Intercept	4.185 (4.009 to 4.360)	46.761	<0.00
Estrogenic	0.045 (0.037 to 0.053)	10.787	<0.00
Ovulation	0.061 (0.05 to 0.072)	10.535	<0.00
Post-ovulation	−0.05 (−0.058 to −0.042)	−12.317	<0.00
Pre-menstrual	−0.135 (−0.144 to −0.127)	−31.937	<0.00
Age	−0.001 (−0.004 to 0.003)	−0.501	0.617
BMI	0.016 (0.013 to 0.019)	9.374	<0.00
Cycle length	0.000 (−0.002 to 0.002)	0.034	0.973

hormonal measurements in our study poses a significant challenge in establishing a clear and direct link between hormonal fluctuations and CO_2 changes, [28, 31]. Future comprehensive studies testing CO_2 changes while incorporating hormonal measurements are needed. The exclusion of hormonal birth control (HBC) users limits our understanding of CO_2 patterns in the context of hormonal intervention of women in childbearing ages, especially since

Table 3. Determinants of CO_2 changes between the different population groups

Phase/parameter	β (95% CI)	*z* statistics	*p* value
Intercept	3.986 (3.877 to 4.095)	71.624	<0.00
Meno with-HRT	−0.083 (−0.113 to −0.053)	−5.436	<0.00
Age	0.005 (0.003 to 0.006)	5.877	<0.00
BMI	0.016 (0.014 to 0.019)	14.893	<0.00

HBC is widely used [32]. However, only 3.3% of the cohort responders identified themselves as HBC users, not providing a substantial population size. This underscores the need for further studies investigating how HBC affects CO_2 and other metabolic biomarkers. The observed decline in CO_2 levels of both menopausal groups is hypothesized to be associated with improvements in lifestyle factors, posing an unexplained phenomenon. Alternatively, other factors such as practice effect could contribute to this trend. Further investigations are warranted to comprehensively understand and address this observation. Additionally, CO_2 levels are known to be impacted by additional factors including macronutrient consumption [33, 34], fasting duration [35], and physical activity [36]. While these factors may have affected the observed CO_2 patterns, they were not controlled for in this study. Moreover, due to the nature of this study, its population may be limited to individuals with similar demographic characteristics, such as age and dietary habits. Additionally, relying on a single measurement device may limit the generalizability of the results to other devices. Users may have dropped out due to app friction, as a result of the need to input the menstruation date periodically and respond to additional requests during app onboarding. Consequently, caution should be exercised when extending these conclusions to a broader population.

In conclusion, this retrospective analysis of CO_2 patterns across different populations provides valuable insights into the dynamic interplay between hormones and metabolism. We suggest that CO_2 monitoring may have relevance in tracking the MC and offers a novel perspective on metabolic changes during menopause, with or without HRT. Future research should delve deeper into these associations and explore the clinical applications of CO_2 monitoring in fertility awareness, women's health, and personalized healthcare.

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Statement of Ethics

In accordance with ethical standards and following a thorough review, this study received an Institutional Review Board (IRB) exemption under category # 2, as detailed in 45 CFR 46.104(d) and BRANY's standard operating procedure, by BRANY SBER IRB on May 09, 2023, BRANY IRB File # 23-119-1476. The need for informed consent was waived by the BRANY SBER IRB Committee.

Conflict of Interest Statement

T. Cramer, S. Yeshurun, and M. Mor are employees of Metaflow Ltd., receive salary from Metaflow Ltd., and hold stock options from Metaflow Ltd. M. Mor is a co-founder of Metaflow Ltd.

Funding Sources

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Author Contributions

T. Cramer, S. Yeshurun, and M. Mor led the design and conception of the study. M. Mor was the principal investigator of the study. T. Cramer led the acquisition of data, conducted data interpretation and analysis, and wrote the first draft of the manuscript. S. Yeshurun contributed to the data analysis. All authors critically revised the manuscript and gave their final approval.

Data Availability Statement

The data used in this study are owned by Metaflow Ltd. and are not publicly available due to proprietary restrictions. However, the insights, findings, and conclusions drawn from the analysis of these data are presented comprehensively in this publication. Further inquiries can be directed to the corresponding author.

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