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Research Letter

Sex Influences Health: Reporting on Female Characteristics Should be Mandatory in Exercise and Physical Activity-Related Diabetes Research

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Tweet – Female-specific physiological characteristics need to be described better in diabetes and exercise research.

In recent years, there has been an increased interest in Precision Medicine in order to provide treatment and disease management that takes into account individual characteristics, lifestyles, and environments. In spite of this movement towards more precise recommendations, physical activity (PA)/exercise research studies involving females with diabetes (both type 1 and type 2) very often fail to account for female-specific physiological factors such as the menstrual cycle (or lack thereof), cycle regularity, use of hormonal contraceptives, menopausal status, and female-specific cardiometabolic risks (e.g., history of pregnancy complications). The menstrual cycle is known for causing changes in insulin sensitivity throughout the cycle [1]. Pregnancy causes insulin resistance, and menopause is associated with relevant changes in carbohydrate, lipid, and protein metabolism [2]. These variables may alter PA/exercise-related blood glucose responses and muscle health. As such, these characteristics warrant greater attention in research studies involving female participants with diabetes.

Researchers leading studies in PA/exercise involving female participants with diabetes may refer to a recent publication outlining methodological considerations when including females in PA/exercise studies [3]. Some of the main recommendations include recruiting female participants based on pre-defined criteria (e.g., menstrual cycle phase [4], use of hormonal contraceptives, menopausal status, use of hormone replacement therapy) much of which can be provided by self-report. Ideally, some of these characteristics (e.g., menstrual cycle phase, menopausal status) can be confirmed retrospectively through biochemical measurement of samples (blood, urine, saliva) collected at the time of study participation [3]. This working guide for standards of practice also proposes clear definitions for terms such as eumenorrhea, anovulatory, luteal phase, oligomenorrhea, hormonal contraceptive users, perimenopause, and post-menopause among others, while also providing guidelines for hormonal reference ranges that could be used to include

or exclude participant data based on these definitions. Where determining menstrual cycle length and specific phases is concerned, the authors suggest tracking and establishing menstrual cycle characteristics for at least two months prior to testing by, at minimum, noting the first and last day of menstruation for each cycle. For those using hormonal contraceptives, it is recommended to report not only the type and regimen of hormonal contraceptive being used, but also report where the user finds themselves in a cycle (e.g., active oral contraceptive pill days, versus inactive/placebo or pill-free days) if this has not been controlled for in the study design.

While some may argue that we do not have enough evidence of the menstrual cycle or menopause affecting blood glucose or other physiological responses to PA/exercise in female participants with diabetes to warrant these measures, we will never have this type of information unless an effort is made to control for, or at minimum characterize, these factors in research studies. While confirming menstrual cycle status by blood sampling may be beyond the budget of certain small studies, documentation of self-reported values should be standard practice. We suggest that these details include average menstrual cycle length (self-reported based on average of last two cycles), menstrual cycle day/phase of experimental testing days (with day 1 being the onset of menses), menopausal status (months/years since last menstrual cycle), and type/timing within the cycle of hormonal contraceptive use.

With rising reports of sex-related differences in both chronic and acute blood glucose responses to exercise [5], it is important to consider other metabolic aspects of female health that may affect these responses and are presently overlooked in most studies. As such, current guidelines for measuring cardiorespiratory fitness and muscle stimulation around PA, and/or obtaining the optimal glycemic benefits from being active, are based on data collected from studies involving only male participants, or mixed-sex cohorts where female participants are generally poorly

characterised. This lack of information may result in imprecise PA/exercise recommendations for females living with diabetes. We suggest that a better reporting of these characteristics become standard in PA/exercise and diabetes research moving forward, to ensure that females with diabetes are able to achieve optimal health benefits of PA/exercise across different stages of their lifespan.

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Conflict of Interest

JEY has received speaker's fees and in-kind research support from Dexcom, speaker's fees from Abbott, and in-kind research support from One Touch. LB has received speaker's fee and in-kind research support from Dexcom, has received honoraria as a member on scientific advisory boards (Novo Nordisk, Oviva). ASB has received speaker's fees from Dexcom. JBG has received in-kind research support from Dexcom. DPZ has received honoraria for speaking engagements from Ascensia Diabetes, Insulet Canada, and Medtronic Diabetes and is on an advisory board for Dexcom.

Author Contributions and Guarantor Statement

All authors discussed the content of this manuscript in person. JEY drafted the letter. All authors approved the final version of this submission.

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