

New Insights Into Ischemic Heart Disease in Women: The Central Role of Coronary Microvascular Dysfunction Current Insights, Diagnostic Advances, And Therapeutic Uncertainties

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Introduction

This viewpoint discusses emerging evidence and the clinical implications of coronary microvascular dysfunction (CMD) in women, offering a focused perspective on pathophysiologic, diagnostic, and therapeutic features that distinguish ischemic heart disease (IHD) in women from that in men. Beyond summarizing available data, we highlight the growing body of evidence supporting CMD as an important and often underrecognized contributor to ischemic symptoms and cardiovascular risk in women. We emphasize key concepts and ongoing controversies without intending to provide definitive therapeutic recommendations.

Ischemic heart disease (IHD) remains a leading cause of morbidity and mortality worldwide.¹ Recent evidence also highlighted sex-based differences in ischemic pathophysiology and vascular aging in women.²

Angina, or an anginal equivalent, results from myocardial ischemia caused by an imbalance between oxygen supply and demand, with the coronary microcirculation playing a central role in regulating myocardial perfusion. Even in the absence of obstructive epicardial coronary disease, coronary microvascular dysfunction can lead to angina, myocardial ischemia, myocardial infarction, and heart failure.^{3,4} Assessment of vascular function, as well as traditional and nontraditional cardiovascular risk factors, is crucial in both sexes.⁵ In women, sex-specific risk factors (Figure 1) should also be considered to help prevent accelerated vascular aging and reduce the risk of future cardiovascular events.^{6,7}

Keywords

Myocardial Ischemia; Microvascular Angina; Microcirculation; Women's Health

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Sex-based disparities are also evident in acute coronary syndromes, in which women more often present with atypical symptoms and experience delays in both seeking and receiving care. These patterns of underrecognition may contribute to subsequent undertesting and failure to identify nonobstructive ischemic mechanisms (e.g., CMD or vasospasm), reinforcing the need for tailored diagnostic pathways and risk stratification in women.⁸

IHD in women has numerous specificities:⁷

- Smaller epicardial coronary arteries, even after adjustment for body surface area and left ventricular mass.
- Higher prevalence of anginal symptoms and their equivalents, such as fatigue, nausea, and vomiting.
- Higher incidence after menopause.
- Greater association with risk factors and comorbidities.
- Higher mortality after acute infarction.

Early atherogenesis is driven by endothelial dysfunction, with impaired vasodilation and vasoconstriction promoting ischemia across clinical presentations.⁵

Risk factors specific to women can arise during reproductive life, including hypertensive disorders of pregnancy, gestational diabetes, and adverse pregnancy outcomes, which are associated with subsequent hypertension, type 2 diabetes, and IHD.^{7,9} In women referred for coronary angiography because of suspected ischemia, a substantial proportion have non-obstructive coronary arteries, and targeted testing often reveals coronary vasomotor disorders (CMD and/or vasospasm).^{3,4} Women are also more likely to present with myocardial infarction with non-obstructive coronary arteries (MINOCA) than men.¹⁰ Reported estimates of the proportion of symptoms explained by microvascular and vasomotor abnormalities in angiography-selected cohorts vary across referral populations and diagnostic methods. They should not be extrapolated to the general population.^{3,4,11} Overall, women's cardiovascular health is influenced by sex-specific factors across the life course (Figure 2), reinforcing the need for tailored prevention and diagnostic strategies.^{6,7}

The Challenges of Diagnosing IHD in Women

Diagnosing the cause of chest pain in women is challenging and is often not accomplished in routine clinical practice.

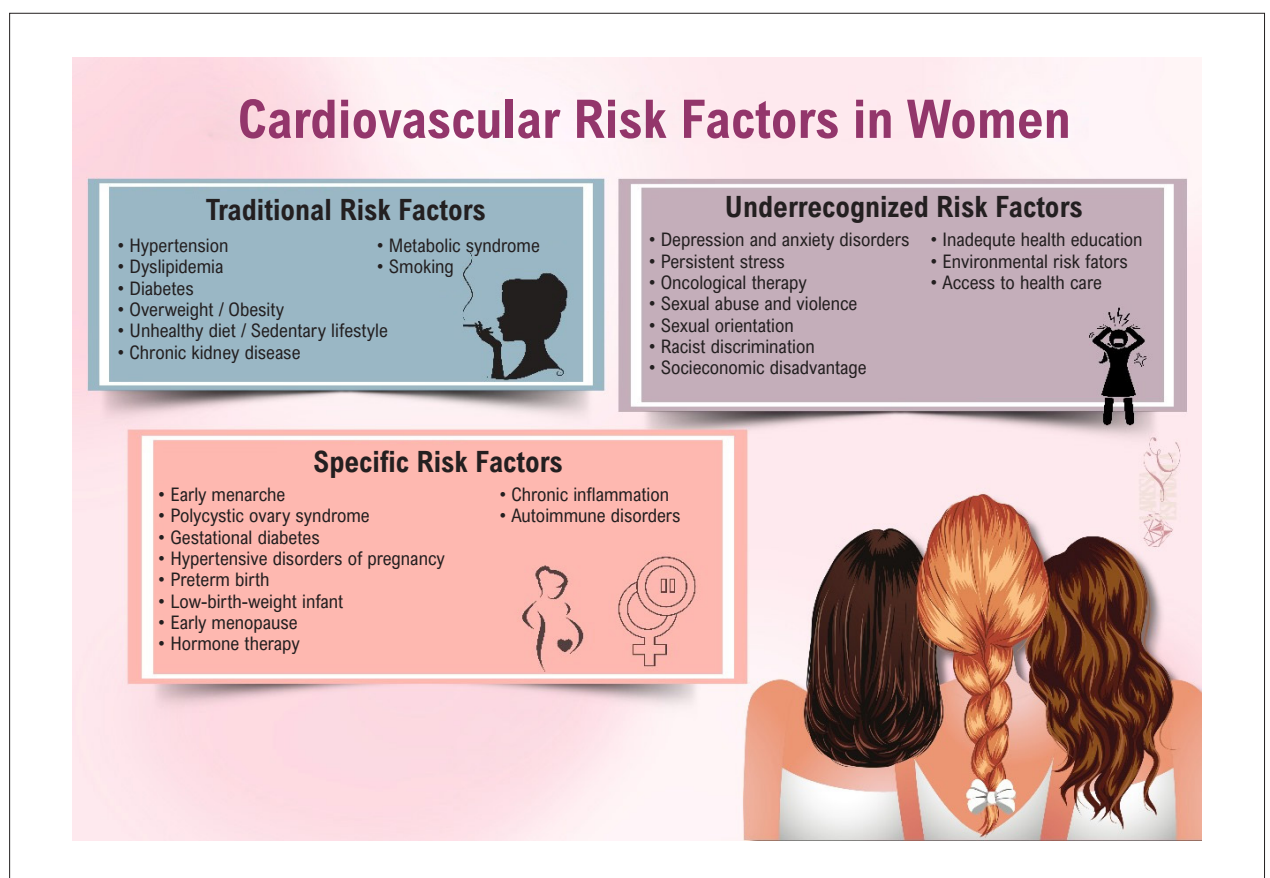


Figure 1 – CV Risk Factors in Women. Adapted from Oliveira et al., 2024.⁶

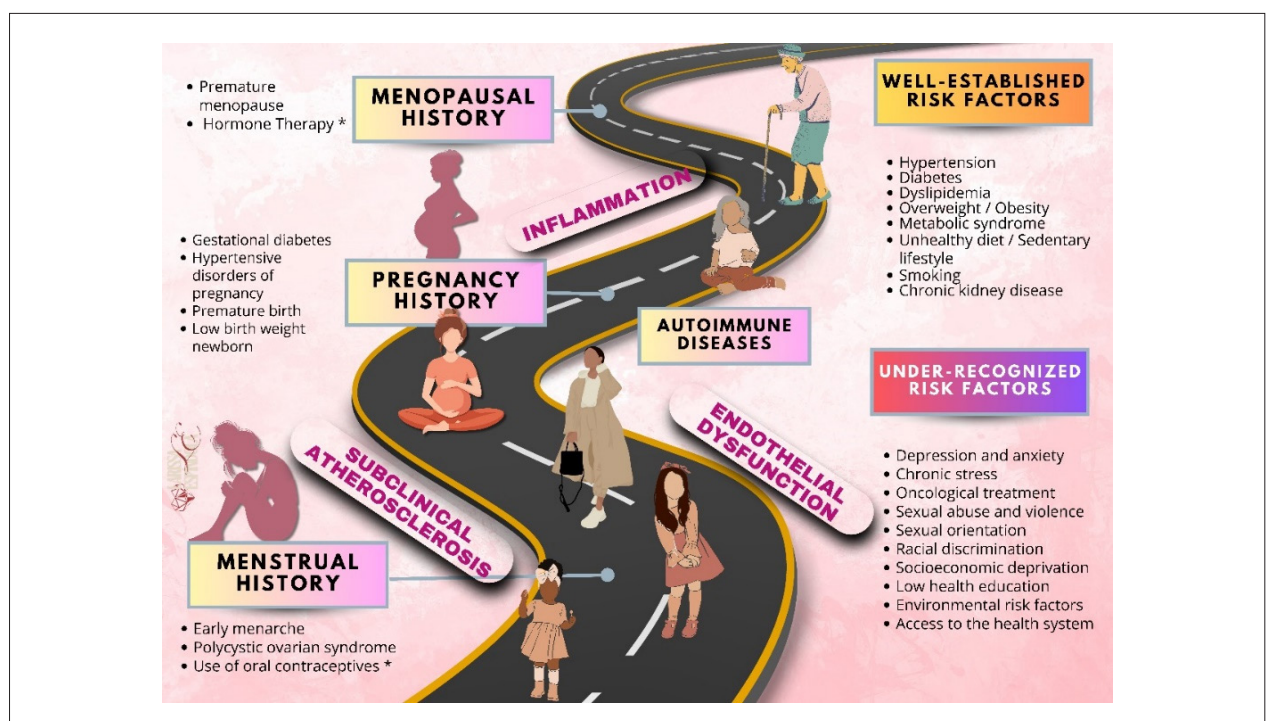


Figure 2 – Women's Cardiovascular Health Journey. Adapted from Oliveira et al., 2024 and Oliveira et al., 2023.^{6,7}

Underdiagnosis may reflect unrecognized atypical symptom patterns, delays in seeking care, and persistent gaps in risk perception and clinical suspicion.¹² Another contributing factor is the high prevalence of ischemia with nonobstructive coronary arteries (INOCA) in women. Contemporary criteria for microvascular angina include ischemic symptoms, the absence of obstructive coronary lesions, objective evidence of ischemia, and evidence of coronary microvascular dysfunction or vasospasm.^{3,4} Documentation of vasomotor disorders using invasive and noninvasive approaches remains the most reliable strategy. PET-based quantification of myocardial blood flow is often considered a reference standard when available, although access and cost limit its widespread implementation.^{3,4} However, PET has been associated with lower use of additional health care resources, with only 25% to 37% of patients undergoing the test requiring further interventions.¹³ Dynamic cadmium-zinc-telluride (CZT) SPECT may also enable noninvasive assessment of myocardial blood flow and is an emerging alternative in some centers.¹⁴ Additionally, pulse wave velocity (PWV) has emerged as a noninvasive marker of arterial stiffness and endothelial dysfunction that may complement the evaluation of systemic vascular health. Although PWV does not diagnose CMD, elevated values may indicate vascular aging and endothelial dysfunction, support overall risk stratification, and prompt consideration of more definitive functional testing when symptoms persist despite nonobstructive angiography.

A practical diagnostic sequence for suspected INOCA is to:

- (1) evaluate symptoms and risk factors,
- (2) exclude obstructive epicardial coronary disease,
- (3) document objective evidence of ischemia when feasible, and
- (4) pursue an endotype-oriented assessment (invasive coronary function testing and/or validated noninvasive measures of coronary flow) to guide mechanism-based therapy and follow-up.^{3,4,15}

Importantly, ischemic syndromes in women often reflect overlapping phenotypes rather than a single mechanism.¹⁶⁻¹⁸ CMD may coexist with epicardial vasospasm, diffuse nonobstructive atherosclerosis, and systemic endothelial dysfunction, and symptom burden may also be influenced by inflammation, autonomic dysregulation, psychosocial stressors, and nonischemic mechanisms of chest pain. Recognizing these interacting endotypes supports more individualized diagnostic pathways and helps avoid overattributing symptoms to CMD alone.^{4,16-18}

Although symptom control is unquestionably highly relevant to the patient's quality of life, clinical evidence indicates that CMD also has important prognostic implications. In this context, assessment of reduced CFR, which can serve as an indicator of microvascular dysfunction, is particularly relevant, as both are associated with a significantly higher incidence of cardiovascular events, including acute myocardial infarction, heart failure, and cardiovascular death, regardless of the presence of obstructive coronary artery disease. This underscores the need for early diagnosis and rigorous therapeutic management beyond pain control.¹⁹

Drug Treatment in INOCA

Management options are summarized in Figure 3.

A phenotype-based approach can help align therapy with the predominant underlying mechanism:

- (1) isolated CMD,
- (2) CMD with concomitant vasospasm, and
- (3) CMD with diffuse non-obstructive atherosclerosis. These phenotypes often overlap and may require combined pharmacologic and lifestyle strategies, with treatment tailored to objective endotyping when feasible.^{4,15}

INOCA treatment is challenging because of its heterogeneous underlying mechanisms and the relative scarcity of randomized trials in women. Current guidance emphasizes mechanism-guided therapy, when endotyping is available, along with aggressive risk factor control and the early use of combination antianginal therapy based on symptom profile and comorbidities.^{4,15,16}

In coronary microvascular dysfunction, vasodilators may have variable efficacy, and treatment often relies on a combination of antianginal agents, such as beta-blockers, calcium channel blockers, ACE inhibitors or ARBs, and statins, together with lifestyle interventions. Long-acting nitrates may provide limited benefit in microvascular angina and may, in some cases, worsen symptoms because of coronary steal.^{4,15}

Recent Guideline Updates – Brazilian Society of Cardiology (2025)

The 2025 Brazilian Guideline for Chronic Coronary Syndrome, published by the Sociedade Brasileira de Cardiologia (SBC), emphasizes the early use of combination antianginal therapy with complementary mechanisms rather than a strictly stepwise escalation. It notes that no single drug class has demonstrated clear superiority for symptom relief or long-term outcomes, supporting a personalized approach that may combine beta-blockers, calcium channel blockers, nitrates, ranolazine, or trimetazidine. This direction is consistent with broader international guidance, including the 2024 ESC guideline on chronic coronary syndromes, which reinforces mechanism-based evaluation and individualized antianginal therapy. This framework is particularly relevant for women with INOCA/CMD and a high symptom burden.^{15,20}

Trimetazidine Use in Microvascular Angina and IHD in Women

Trimetazidine is an established treatment for angina pectoris in IHD and CCS, improving exercise tolerance and quality of life without significantly affecting blood pressure or heart rate.²¹ Its mechanism of action involves shifting myocardial energy metabolism from fatty acid oxidation toward glucose oxidation (Figure 4). This effect occurs through inhibition of fatty acid β -oxidation, thereby increasing glucose oxidation and reducing intracellular lactate accumulation, which helps minimize intracellular acidosis and preserve cell membrane integrity.²²

In women with INOCA/CMD, the overall evidence remains limited and is based largely on small studies and physiologic end points. However, trimetazidine has shown promising results in some clinical studies. In the PATMOS study, which included patients with stable coronary artery

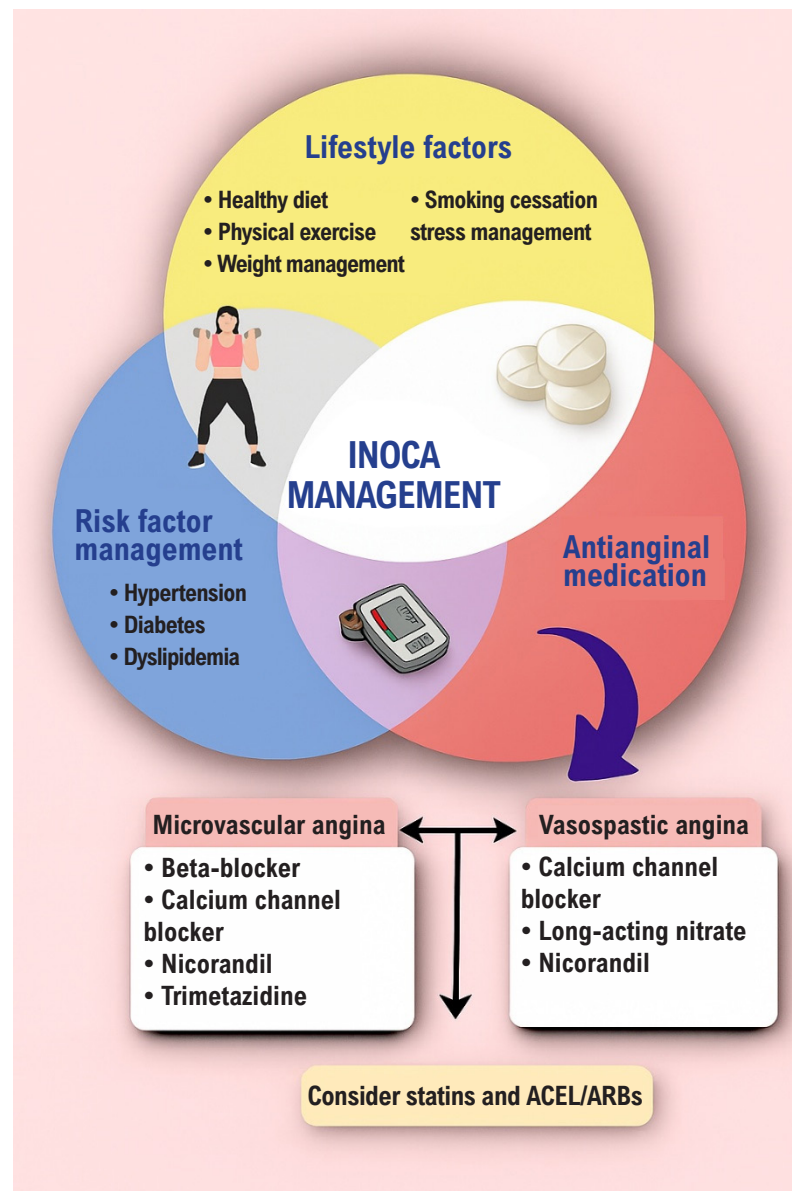


Figure 3 – Overview of pharmacologic and nonpharmacologic management strategies for INOCA. Adapted from Bairey Merz et al., 2017 and Oliveira et al., 2024.^{3,6}

disease undergoing elective PCI, trimetazidine was associated with improvements in physiologic indices of the coronary microcirculation, such as the index of microcirculatory resistance (IMR) and coronary flow reserve (CFR).²³ A small randomized study by Bol'dueva et al. also reported symptom improvement in patients with microvascular angina treated with trimetazidine.²⁴ Accordingly, current guidelines position trimetazidine as an antianginal option across nine of ten patient profiles, cite the 80 mg formulation as favorable for adherence, and emphasize early combination strategies tailored to phenotype and symptom burden.²⁰ In addition, the

Position Paper on IHD in Women recognizes trimetazidine as a key pharmacologic treatment option.^{6,7}

Key evidence gaps include the absence of randomized trials specifically focused on women with INOCA, the limited external validity of existing studies, and the lack of hard clinical end points, such as myocardial infarction, hospitalization, and mortality. For this reason, metabolic or antianginal agents such as ranolazine and ivabradine, as well as nicorandil in vasospastic phenotypes, should be viewed within the same critical framework: symptom-focused options that require more robust comparative data and outcome-based trials.^{4,15-18}

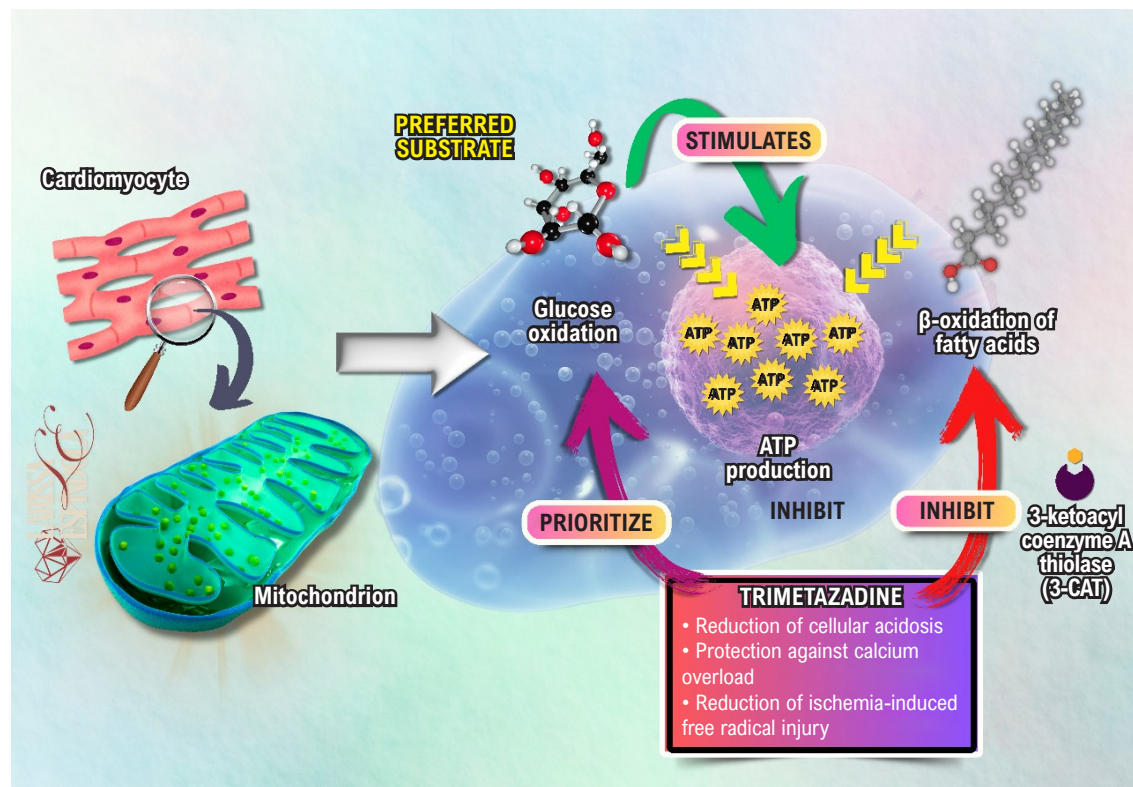


Figure 4 – Mechanism of Action of Trimetazidine. Adapted from Marzilli et al., 2019.²²

Conclusion

Women face distinct pathophysiologic, diagnostic, and therapeutic challenges in ischemic heart disease, with coronary microvascular dysfunction emerging as a key contributor to symptoms and cardiovascular risk. Recognizing sex-specific risk factors, ranging from reproductive conditions to menopause, remains essential for timely diagnosis, prevention, and individualized care.

Contemporary guidelines, including the 2025 SBC update and the ESC chronic coronary syndrome framework, emphasize the early use of combination antianginal therapy with complementary mechanisms, guided by patient profile rather than stepwise escalation of monotherapy. Metabolic modulators and other agents may be considered for selected INOCA/CMD phenotypes; however, evidence in women remains heterogeneous, and outcome-driven trials are still needed to refine precision-based approaches. This viewpoint highlights current concepts and controversies and should not be interpreted as providing definitive therapeutic recommendations.

Notes

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Author Contributions

Conception and design of the research, writing of the manuscript: Alexandre ERG, Salomão I, Penalva R, Mesquita CT, Silva ML; obtaining financing: Silva ML; critical revision of the manuscript for intellectual content: Alexandre ERG, Salomão I, Espíndola LN, Penalva R, Mesquita CT, Silva ML; article illustration: Espíndola LN.

Potential Conflict of Interest

Alexandre ERG, Salomão I, Espíndola LN, Penalva R and Mesquita CT received educational support from Servier. Silva ML is an employee of Servier.

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Study Association

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This article does not contain any studies with human participants or animals performed by any of the authors.

Use of Artificial Intelligence

During the preparation of this work, the author(s) used Chat GPT for correcting grammar and improve text style. After

using this tool/service, the author(s) reviewed and edited the content as needed and take full responsibility for the content of the published article.

Availability of Research Data

The underlying content of the research text is contained within the manuscript.

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