

Commentary

Sex as a Missing Moderator in the Dual-Pathway Neuroprotection Hypothesis

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ABSTRACT: The Dual-Pathway Neuroprotection Hypothesis, recently proposed by Badea and colleagues, distinguishes voluntary from enforced exercise and links each to distinct neural pathways, moving beyond the unitary view of exercise as a homogeneous intervention. However, the hypothesis does not consider sex as a biological variable. Given that AD is a sex-biased disease affecting approximately 65–70% women, and that the neuroprotective effects of exercise are sexually dimorphic, we argue that sex may function as a critical moderator of this framework. We propose three testable predictions: (1) voluntary exercise's cortico-limbic effects may be potentiated in females through estrogen-BDNF signaling, but this effect may be constrained by menopausal status; (2) structured/supervised exercise may yield sex-divergent outcomes—with preliminary observations suggesting A β clearance in females versus neurotrophic upregulation in males—though evidence remains preliminary and derives from a limited number of heterogeneous studies; and (3) stress burden may reduce the net benefit of enforced exercise, but this will require direct testing. These predictions converge on a formal revision in which sex is not a confounder to be controlled for, but a core biological moderator that may moderate modality-specific neuroprotection. This extended model provides a hypothesis-generating framework for designing future sex-aware exercise studies in AD, but does not yet support sex-stratified clinical prescriptions. This framework is predominantly based on preclinical and indirect evidence from heterogeneous models, necessitating cautious interpretation and rigorous validation.

Keywords: Alzheimer's disease, sex differences, voluntary exercise, enforced exercise, neuroprotection, exercise prescription

Introduction

Alzheimer's disease (AD) remains one of the most pressing public health challenges of our time. Although disease-modifying therapies (e.g., anti-A β monoclonal antibodies) have recently emerged, their benefits remain limited, eligibility criteria are narrow, and safety concerns persist—realities that have intensified interest in lifestyle-based preventive strategies. Among these, physical exercise stands out as one of the most promising non-pharmacological strategies. Yet a paradox persists: although exercise is widely recommended for AD prevention, we have only a rudimentary understanding of how it confers neuroprotection—largely because most

studies have treated exercise as a homogeneous intervention, ignoring that not all exercise is the same and not all individuals respond the same way.

The recent study by Badea and colleagues represents a significant advance in this regard [1]. Using a familial AD mouse model, the authors demonstrated that voluntary and enforced exercise engage fundamentally distinct neural pathways. Voluntary exercise predominantly increased cortico-limbic volumes (hippocampus, cingulate, entorhinal cortex) and enhanced cerebral blood flow in motor cortex and hippocampus. Enforced exercise, by contrast, chiefly influenced subcortical and sensory regions, including thalamus and brainstem. Connectivity analyses confirmed modality-

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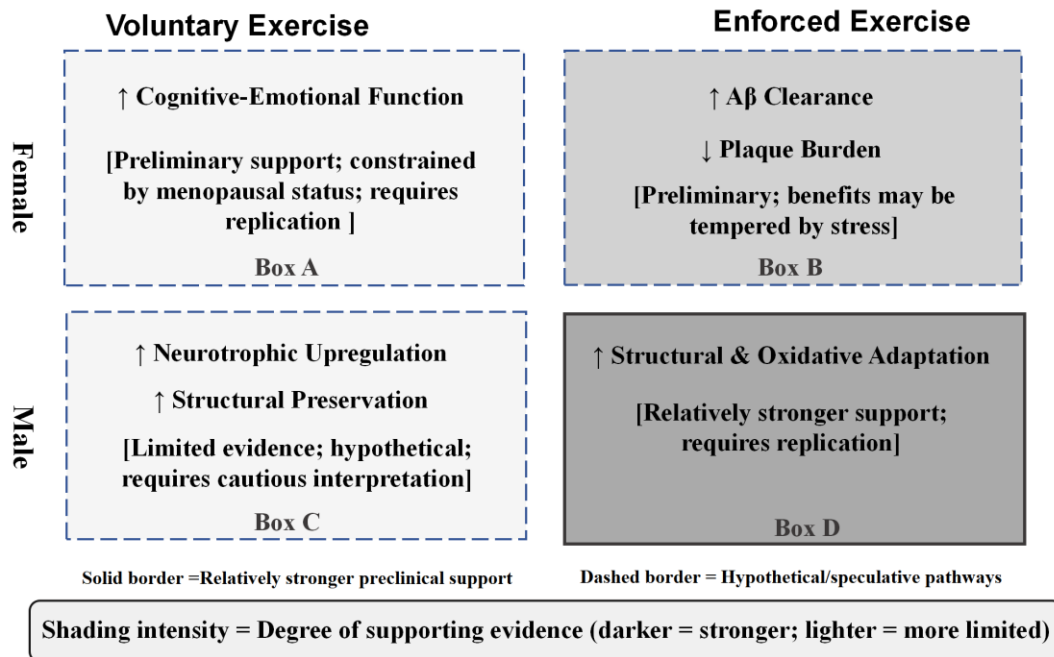
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specific network engagement—predominantly cortico-limbic in voluntary exercisers and subcortical-sensorimotor in enforced exercisers [1]. The authors term this framework the Dual-Pathway Neuroprotection Hypothesis.

This is an elegant and clinically consequential framework. By moving beyond the unitary view of

exercise as a homogeneous intervention, it opens the door to type-specific, individualized exercise prescription in AD rehabilitation, a paradigm shift from one-size-fits-all to precision rehabilitation. However, the hypothesis contains a notable gap: it does not consider sex as a biological variable.

Sex as a Biological Moderator of the Dual-Pathway Neuroprotection Hypothesis



Important: All pathways are conceptual and hypothesis-generating. This figure should not be interpreted as representing established mechanisms or as a basis for clinical recommendations.

Figure 1. A 2×2 conceptual matrix of the proposed sex-by-exercise-modality interaction in AD neuroprotection. Solid lines denote pathways with relatively stronger preclinical support; dashed lines denote hypothetical or speculative pathways with limited or conflicting evidence. Shading intensity indicates the degree of supporting evidence (darker shading = relatively stronger evidence; lighter shading = more limited or speculative evidence)—and this differentiation is also conveyed through line style (solid vs. dashed) to ensure accessibility for color-blind readers. The matrix explicitly includes all four sex-modality combinations: Box A (voluntary-female), Box B (enforced-female), Box C (voluntary-male), and Box D (enforced-male), along with key moderators (estrogen, stress, APOE4, menopausal status) that may influence each pathway. **Important:** All pathways and relationships depicted in this figure are conceptual and hypothesis-generating; none should be interpreted as established mechanisms. The strength of evidence varies substantially across quadrants: Box A (voluntary-female) is constrained by postmenopausal estrogen decline and will require direct testing in aged and ovariectomized models; Box C (voluntary-male) is informed by Short et al.'s finding that BDNF upregulation does not guarantee behavioral rescue—highlighting that BDNF-based predictions will require cautious interpretation across sexes; Box B (enforced-female) is supported by preliminary Aβ clearance findings from a single resistance exercise study, though these observations will require replication and may be tempered by stress-related confounds; Box D (enforced-male) is supported by preliminary neurotrophic upregulation findings from resistance exercise studies, also will require replication. This figure is intended to illustrate hypothesized relationships to guide future research and should not be interpreted as representing established mechanisms or as a basis for clinical recommendations.

This omission is consequential for at least three reasons. First, AD itself is a sex-biased disease. Women

represent approximately 65–70% of the total AD population [2], a figure partly attributable to women's

longer life expectancy, though biological susceptibility also plays a role (Fig. 1). Compared with men, women diagnosed with mild AD may experience faster disease progression in the early stage. At the pathological level, women exhibit greater hippocampal A β accumulation and neurofibrillary tangle density, more rapid advancement through Braak stages, and—particularly among APOE4 carriers—more pronounced pathological burden [3,4]. A scoping review of physical activity and AD risk found that most studies (80%) reported significant results for females, with some studies finding that physical activity can reduce AD risk in women but not in men [5]. Second, the neuroprotective effects of exercise are themselves sexually dimorphic. A growing body of evidence indicates that biological sex may be an important moderator of the relationship between physical activity and cognition [6,7]. As Dong and colleagues systematically documented in their recent comprehensive review (which, despite its use of the term "gender," primarily examined biological sex-related differences), exercise in women is more strongly associated with improvements in cognitive function, neurotrophic support, and emotional regulation; in men, benefits tend to involve structural preservation and oxidative adaptations [2]. A systematic review and meta-analysis further reported that exercise, especially treadmill exercise, swimming, and voluntary wheel running, significantly increased BDNF levels in hippocampus and cortex of AD models, with swimming being the most effective intervention type [8]. Third, and most critically for the Dual-Pathway Hypothesis, the molecular pathways through which voluntary and enforced exercise are proposed to operate are precisely those known to exhibit sex differences—BDNF signaling, stress responses, and neurotrophic regulation. This observation motivates our proposal, but it also necessitates careful terminological distinctions between animal and human exercise paradigms, which we articulate below.

Before articulating our predictions, a terminological clarification is warranted. In the original Dual-Pathway framework as defined by Badea and colleagues, “voluntary” exercise refers to self-initiated, intrinsically motivated activity (e.g., free wheel running in rodents, self-directed aerobic exercise in humans), whereas “enforced” exercise refers to externally imposed, structurally prescribed activity (e.g., forced treadmill running in rodents, supervised rehabilitation protocols in humans). However, we acknowledge that human resistance training—though often externally structured—is typically performed with informed consent and active participation and thus should not be automatically equated with “enforced” exercise in the rodent sense. To avoid conflation, we adopt the following operational definitions throughout this commentary: (1) voluntary/unstructured

exercise: self-paced, intrinsically motivated activity; (2) structured/supervised exercise: externally prescribed but voluntarily undertaken (e.g., human resistance training, supervised aerobic programs); and (3) forced/involuntary exercise: externally imposed without volitional control (primarily rodent paradigms). Importantly, throughout this commentary, human interventions, including resistance training and supervised rehabilitation programs, are consistently referred to as ‘structured’ or ‘supervised’ exercise, never as ‘enforced’ or ‘involuntary’. Where we cite studies using resistance training as indirect evidence for the enforced pathway, we explicitly acknowledge that these represent structured rather than truly forced exercise. This distinction does not undermine the comparison, as the key neurobiological distinction between the two modalities lies not in the presence of external resistance per se, but in whether movement is self-initiated versus imposed by external protocols.

Sex as a Potential Moderator of the Dual Pathways of Exercise

We propose that sex functions as a critical moderator of the Dual-Pathway Neuroprotection Hypothesis—systematically modulating the magnitude, and potentially the direction, of the modality-specific effects that Badea and colleagues observed. This argument generates three specific, testable predictions, which together converge on a formal revision of the original framework.

Prediction 1: Voluntary exercise may preferentially benefit females via estrogen–BDNF potentiation, but this effect may be constrained by hormonal status

The voluntary exercise pathway, as articulated in the original hypothesis, operates through intrinsic motivation activating the mesolimbic reward system, which in turn upregulates BDNF expression via CREB-mediated transcription, promoting cortico-limbic plasticity. Estrogen signaling has been reported to enhance BDNF transcription via estrogen receptor binding to estrogen response elements (EREs) in the BDNF gene promoter [9] and to potentiate TrkB signaling, thereby amplifying the neurotrophic response to synaptic activity [10]. However, this mechanistic cascade has been predominantly characterized in young or middle-aged female rodents, and its applicability to the postmenopausal state—which characterizes the vast majority of women with AD—remains unclear.

Critically, the decline in estrogen levels during perimenopause and postmenopause impairs the clearance of A β and phosphorylated tau and may attenuate the very BDNF potentiation that underlies the predicted female advantage [11]. This suggests a constrained window hypothesis: estrogen-BDNF amplification of voluntary

exercise effects may be most pronounced in premenopausal or perimenopausal females, but this advantage may diminish or disappear in the postmenopausal state. Consistent with this, Barha and colleagues found that aerobic exercise improves executive functions in females, but not males, in the absence of the BDNF Val66Met polymorphism [6]—an effect observed in older adults who are predominantly postmenopausal, suggesting that some BDNF-mediated effects may persist even after menopause, albeit potentially attenuated.

A key piece of evidence that complicates a simple estrogen-BDNF narrative comes from Short and colleagues, who found that while chronic voluntary wheel running elevated hippocampal *Bdnf* mRNA in both aged male and female mice, it rescued cognitive flexibility exclusively in males [12]. The female mice in this study were perimenopausal (11 months of age), and despite showing exercise-induced *Bdnf* upregulation comparable to males, they derived no cognitive benefit. This dissociation between molecular upregulation and behavioral rescue in perimenopausal females suggests that estrogen-BDNF signaling may become functionally decoupled from cognitive outcomes in the aging female brain—a finding that does not support, and in fact challenges, the notion that voluntary exercise preferentially benefits females through BDNF-dependent mechanisms. We therefore propose that the female advantage in the voluntary pathway, if it exists, may be conditional on hormonal milieu, age, and menopausal stage, and will require direct testing in postmenopausal AD models.

A critical caveat: menopausal status as a biological confound. The predictions articulated above should be interpreted with caution given that AD predominantly affects older, postmenopausal women. The estrogen-BDNF potentiation mechanism proposed in Prediction 1 has been primarily characterized in young or cycling female rodents; its relevance to the postmenopausal state—characterized by ovarian hormone depletion, altered estrogen receptor expression, and potentially blunted BDNF responsiveness—remains largely unestablished. Mechanistically, ovariectomized (OVX) animal models have shown that estrogen loss attenuates exercise-induced BDNF upregulation and hippocampal neurogenesis [11], suggesting that the female advantage may be lost after menopause. Conversely, hormone replacement therapy may restore some of these effects [11], but the interaction among exercise, hormone therapy, and AD pathology is complex and remains incompletely characterized. We therefore emphasize that biological sex should not be treated as a simple surrogate for estrogen exposure, and that future mechanistic studies must incorporate aged, OVX, and postmenopausal models to directly test the hormonal

dependency of the proposed sex-by-modality interactions. This limitation is not unique to our framework—it is a systemic gap in the exercise-neuroprotection literature—but it is essential to acknowledge it explicitly.

Prediction 2: Structured/supervised exercise may yield sex-divergent outcomes—with preliminary observations suggesting A β clearance in females versus neurotrophic upregulation in males—though evidence remains preliminary and derives from heterogeneous studies

The enforced exercise pathway, as originally defined by Badea and colleagues, engages sensorimotor systems, leading to enhanced perfusion in subcortical structures (thalamus, brainstem) and strengthening of sensorimotor networks. In considering the translatability of this pathway to human contexts, we draw upon evidence from structured/supervised exercise paradigms. Some of the available evidence for sex-specific effects in this domain of structured/supervised exercise comes from Azevedo and colleagues, who investigated the long-term effects of resistance exercise in male and female APP/PS1 mice [3]. Although this study examined resistance exercise rather than forced treadmill running—and resistance exercise in humans is typically voluntary and structured rather than truly forced—it provides useful indirect evidence for how externally prescribed exercise may produce sex-divergent outcomes. Neurobiologically, the distinction between self-initiated and externally prescribed activity is relevant, though we acknowledge that human resistance training should not be equated with rodent forced exercise (see Operational Definitions above). Their findings thus offer the closest available evidence for sex-specific effects in the domain of structured/supervised exercise. After a 4-month resistance exercise protocol, female APP/PS1 mice showed reduced hyperlocomotion, rescued short-term memory, increased VEGF levels, and—critically—reduced brain A β and plaque burden. Male APP/PS1 mice, by contrast, rescued learning and long-term memory, increased IGF-1 and BDNF levels, but showed no significant reduction in A β or plaque burden [3].

However, these findings derive from a single resistance training study in APP/PS1 mice, and the apparent dissociation—A β clearance in females versus neurotrophic upregulation in males—has not yet been directly replicated in other AD models or under truly forced exercise paradigms. This pattern should therefore be viewed as a preliminary observation requiring replication and mechanistic validation, rather than as an established sex-specific mechanism.

It is important to acknowledge that resistance training—the primary source of evidence for sex-divergent outcomes in this domain—differs from forced treadmill paradigms in several fundamental aspects. First, volitional control: resistance training in humans is

voluntary and self-initiated, whereas forced treadmill running in rodents is externally imposed without the animal's volitional participation. Second, stress exposure: forced paradigms may introduce stress-related confounding (e.g., elevated glucocorticoids, aversive motivational states) that is substantially less pronounced in voluntary resistance training. Third, intensity and energetics: resistance training involves high-load, low-repetition muscle contractions with intermittent rest periods, whereas forced running entails sustained, repetitive aerobic effort with different metabolic and cardiovascular demands. Fourth, motor and neural demands: resistance training emphasizes motor unit recruitment, strength development, and proprioceptive feedback, whereas forced running engages stereotyped locomotor patterns. These differences limit the direct translatability of resistance training findings to the enforced exercise pathway as defined in the original Dual-Pathway framework. Therefore, while Azevedo and colleagues' findings offer valuable indirect evidence—and represent the best available data on sex-specific effects of structured exercise in AD models—they should not be interpreted as direct confirmation of the enforced exercise pathway.

Complementing these findings, Hall and colleagues recently demonstrated in the TgF344-AD rat model that exercise neuroprotection exhibits a clear sex difference, with females showing greater cognitive and pathological benefits from exercise intervention [13]. This finding is consistent with the observations in APP/PS1 mice and suggests that sex-dependent exercise effects may be reproducible across different AD models, though further replication is needed. Zhou and colleagues further reported that treadmill running in APP/PS1 mice produced significantly greater increases in white matter volume and myelinated fiber parameters in females compared to males, suggesting that structured aerobic exercise may induce sex-specific structural effects in rodent models [14]. However, these findings derive from a forced running paradigm in animals and should not be directly extrapolated to human structured exercise without further investigation. This dissociation is noteworthy and is consistent with the view that sex may moderate the pathway through which exercise confers neuroprotection, though direct evidence in truly forced paradigms remains limited. Notably, a review on sex differences in AD biomarkers according to exercise types reported that resistance exercise may induce sex-specific IGF-1 responses, with greater increases observed in women [15], which is broadly consistent with the molecular basis of this hypothesized sex-divergent pattern.

Prediction 3: Stress burden may reduce the net benefit of enforced exercise, but this effect will require direct testing

Badea and colleagues acknowledge that enforced exercise protocols may introduce stress-related confounding. This is not a trivial methodological concern—it is a biologically meaningful variable that may interact with sex in potentially predictable ways. Some studies have reported that females may exhibit greater HPA axis reactivity to certain stressors, although this response is highly dependent on species, age, stressor type, chronicity, and the specific outcome measured [16]. For instance, forced exercise paradigms in rodents have been shown to introduce stress-related confounding that may mitigate some of the beneficial effects of physical activity in AD models [17]. Belviranlı and Okudan further compared voluntary, involuntary, and forced exercise in an experimental AD model and found that all three modalities almost equally reversed behavioral impairment by regulating hippocampal neurotrophic factors and oxidative stress [18].

However, extrapolating from human depression prevalence to exercise-induced physiological stress responses in AD models is not straightforward. We therefore reframe Prediction 3 as a testable hypothesis: if enforced paradigms in animals elevate glucocorticoids to a greater extent in females under specific experimental conditions, then the net neuroprotective effect may be attenuated in females relative to males. This prediction will require direct testing with sex-specific stress biomarkers (corticosterone, adrenal weight, anxiety-like behaviors) in AD models, rather than being assumed *a priori*.

Integrating Sex into the Dual-Pathway Model: A Formal Revision

Collectively, these three predictions converge on a formal revision of the Dual-Pathway Neuroprotection Hypothesis. We propose the following hypothetical extended framework: voluntary exercise may preferentially engage cortico-limbic networks, and this engagement could hypothetically be potentiated in females through estrogen-BDNF interactions, though this may be constrained by menopausal status. Structured/supervised exercise may preferentially engage subcortical-sensorimotor networks, and this pathway could yield sex-divergent outcomes—with preliminary evidence suggesting A β clearance and cognitive rescue in females versus neurotrophic upregulation and structural preservation in males [3,11,14]—but this pattern will require replication and mechanistic verification, and direct evidence remains limited. The net benefit of each modality might be further modulated by hypothesized sex differences in stress sensitivity, though this will require empirical verification. Studies such as Choi and colleagues have demonstrated that forced exercise

paradigms can introduce stress-related confounding that may mitigate some of the beneficial effects of physical activity in AD models [17], but whether this confound operates in a sex-dependent manner remains to be directly tested. In this extended model, sex is not a confounder to be controlled for, but a core biological moderator that may shape modality-specific neuroprotection in ways that require further investigation. We emphasize that these proposals are hypothesis-generating and will require rigorous experimental testing.

Implications for Future Clinical Trial Design (Not Current Clinical Practice)

The framework proposed here has implications for future research design rather than immediate clinical prescription. We explicitly caution against translating these predictions into sex-specific exercise recommendations at the present stage, and we emphasize that human interventions should always be described as ‘structured’ or ‘supervised’ rather than ‘enforced’. The current evidence base—predominantly preclinical, heterogeneous in exercise protocols, and limited in postmenopausal female models—is insufficient to support sex-stratified clinical exercise prescriptions for AD patients.

Instead, we suggest the following translational approach: (1) future randomized controlled trials of exercise in AD should be designed with sex as a stratifying variable and sufficient power to detect sex-by-modality interactions; (2) secondary analyses of existing large-scale trials (e.g., FINGER, EXERT) should examine whether exercise effects differ by sex and menopausal status [19]; (3) in clinical practice, exercise prescription should prioritize individual-level factors—preference, adherence, stress tolerance, frailty, cardiovascular capacity, disease stage, and cognitive status—over biological sex. Sex may be one of many relevant moderators, but the proposed framework is not yet ready to determine treatment selection. Clinically, the most prudent approach is to offer both voluntary and structured exercise options, monitor individual response, and adjust based on tolerance and preference, rather than assigning exercise modalities based on sex alone.

Three Research Priorities to Test the Extended Framework

Three research priorities emerge from this framework. First, the original neuroimaging data from Badea and colleagues should be re-analyzed with sex as a stratifying variable—a high-feasibility, low-cost step that could immediately test whether the modality-specific network effects differ between sexes. Second, existing human AD

exercise trials should undergo sex-stratified secondary analyses, with particular attention to menopausal status and APOE4 genotype. Third, future mechanistic studies must incorporate ovariectomized and aged female animal models to directly test whether the estrogen-BDNF potentiation of voluntary exercise effects is preserved, attenuated, or lost in the postmenopausal state.

Beyond sex, APOE4 genotype—the strongest genetic risk factor for late-onset AD—adds another layer of complexity. APOE4 accounts for nearly 50% of the genetic risk for late-onset AD, with greater effects in females [20]. Recent evidence suggests that the interaction between exercise modality (in both animal and human studies) and sex may be further moderated by APOE genotype [21], and ten-year longitudinal data indicate that higher physical activity is linked to slower precuneus atrophy in older women with APOE4 [22]. Furthermore, genome-wide pleiotropic analyses have revealed that the genetic architecture underlying the relationship between AD and physical activity is fundamentally sex-dependent [23]. These findings reinforce the need for sex-stratified approaches in future studies, though a full integration of APOE4 into the current framework is beyond the scope of this commentary.

Conclusion

The Dual-Pathway Neuroprotection Hypothesis provides a useful framework for understanding how exercise confers neuroprotection in Alzheimer’s disease. By distinguishing voluntary from enforced exercise and linking each to distinct neural pathways, it provides a framework for moving beyond one-size-fits-all exercise prescription toward truly individualized rehabilitation strategies. However, any framework that describes pathways of neuroprotection must account for who is traversing them. Sex is not merely a demographic variable—it may be an important neurobiological moderator of AD pathology, exercise responses, and the very neural circuits through which exercise exerts its effects. Incorporating sex into the Dual-Pathway framework is not an optional refinement; it is a necessary step toward a complete theoretical framework that can guide future research—and ultimately, as evidence accumulates, inform evidence-based approaches to exercise-based neuroprotection in Alzheimer’s disease.

Nevertheless, we emphasize that the predictions advanced here remain predominantly hypothesis-generating and will require rigorous testing in aged, postmenopausal, and ovariectomized animal models, as well as in sex-stratified human trials, before they can inform clinical practice. At present, the most clinically responsible approach is to monitor individual

adherence, stress responses, and functional outcomes rather than to prescribe exercise based on sex alone. Recognizing this dimension does not diminish the elegance of the original framework—it strengthens it by grounding it in the biological reality of the diverse populations we seek to understand and ultimately treat, while underscoring the need for sex-aware research design rather than premature clinical stratification.

Authors' Contributions

All authors contributed to the conception, writing, and revision of this manuscript. Zehui Gong drafted the original manuscript. Jianrong Yuan and Liang Xiang critically revised the manuscript for important intellectual content. Zhaobing Xiang provided administrative and supervisory support. All authors read and approved the final manuscript.

Conflicts of Interest

The authors declare no conflicts of interest.

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