

1 Running head: Exercise Neurophysiology in Migraine in Females

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3 Resistance training for migraine in females: mechanistic review of hormonal, CGRP, autonomic, vascular and
4 nociceptive pathways

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17 **ABSTRACT**

18 Migraine is the second leading cause of years lived with disability worldwide and disproportionately affects
19 women, in whom the disorder tends to be more frequent, longer-lasting and functionally more disabling than in
20 men. This female preponderance, which emerges after menarche, is tightly linked to changes in estrogen levels,
21 reproductive phases and sex-specific responsiveness of the trigeminovascular and calcitonin gene-related
22 peptide (CGRP) systems. Against this backdrop, non-pharmacological interventions that modulate the same
23 physiological processes involved in migraine are particularly attractive. Resistance training (RT) has emerged

from recent systematic reviews and network meta-analyses as one of the exercise modalities with the largest effect sizes on monthly migraine frequency, yet its mechanistic rationale in women is rarely addressed as a coherent biological argument. In this narrative review we integrate the pathophysiology of migraine in females with the adaptations induced by structured RT across four convergent axes: autonomic regulation, neurovascular and endothelial function, systemic and neurogenic inflammation, and endogenous pain modulation. We interpret the current clinical evidence in light of these mechanisms, outline how the hormonal milieu in females may shape individual responsiveness, and propose a translational framework for prescribing RT as part of a comprehensive, sex-informed migraine management plan. We explicitly distinguish between robust findings, emerging signals and hypotheses that remain to be tested, and highlight the main methodological barriers that should be addressed before RT can be firmly embedded in clinical guidelines for women with migraine.

Keywords: calcitonin gene-related peptide; estrogen; exercise; migraine; resistance training; women

INTRODUCTION

Migraine is a highly prevalent, genetically influenced and episodically to chronically disabling neurological disorder with prominent trigeminovascular and neurovascular components that affects more than one billion individuals globally, with a pronounced female preponderance from puberty onward [1–3]. In the Global Burden of Disease framework, migraine consistently ranks among the leading causes of years lived with disability in women of reproductive age, accounting for substantial occupational, domestic and psychosocial costs that extend well beyond the ictal phase [1,4]. Although the 2018 approval of monoclonal antibodies targeting CGRP and its receptor, and the more recent incorporation of small-molecule gepants, have markedly expanded the pharmacological armamentarium, access, tolerability, comorbidity management and patient preference continue to motivate the search for non-pharmacological strategies with strong mechanistic underpinnings [5–7].

The greater vulnerability to migraine observed in females is not accidental. Its temporal expression follows reproductive milestones with remarkable fidelity: incidence rises sharply after menarche, peaks in the third and fourth decades, attenuates during high-estrogen pregnancy, and fluctuates again across perimenopause and menopause [3,8,9]. Converging clinical, endocrine and

50 neurophysiological data implicate cyclical estradiol withdrawal, modulation of estrogen receptor
51 signaling in trigeminovascular structures, and sex-biased responsiveness of the CGRP pathway as
52 core nodes of this dimorphism [2,10–13]. Any rational non-pharmacological strategy aimed at
53 reducing migraine burden in women must therefore address, rather than bypass, these sex-related
54 biological pathways.

55 Among non-pharmacological options, structured physical exercise has accrued increasing empirical
56 support. Moderate aerobic exercise has the longest evidence base among exercise modalities, supported by
57 randomized trials and recent dose-response and network meta-analyses [14,15]. More recent network meta-
58 analyses, however, reposition resistance training (RT) as at least equivalent, and in several comparisons
59 superior, to aerobic modalities for reducing monthly migraine days, with combined aerobic plus resistance
60 protocols yielding the largest pooled effect [15,16]. This evolving evidence base raises a physiologically
61 pertinent question: why should loading skeletal muscle influence a trigeminal-cortical disorder, and how do the
62 resulting adaptations interact with the female hormonal milieu that shapes migraine vulnerability?

63 This narrative review integrates three strands of literature that are usually discussed separately.
64 First, we revisit the hormonal and peptidergic biology of migraine in women, with emphasis on the
65 estrogen- CGRP interface and its translational consequences. Second, we map the physiological
66 adaptations induced by progressive RT onto the key migraine substrates (i.e., autonomic tone,
67 endothelial function, inflammatory set-point and endogenous pain inhibition). Third, we interpret the
68 current clinical evidence, including the latest network and dose–response meta-analyses, through this
69 mechanistic lens. The goal is not to champion RT as a universal therapy, but to articulate a sex-
70 informed biological rationale and a cautious translational framework that can guide both clinicians and
71 future trialists. Accordingly, this review is deliberately focused on adult women and on resistance
72 training as a mechanistically distinct exercise modality. It does not aim to provide a comprehensive
73 synthesis of purely aerobic exercise mechanisms, pediatric or adolescent migraine, or migraine in
74 men. These populations and modalities are discussed only where they help contextualize the sex-
75 informed biological rationale for RT.

76 **EPIDEMIOLOGY AND CLINICAL BURDEN IN WOMEN**

77 Population-level estimates consistently report one-year prevalences of migraine of approximately
78 18–22% in women and 6–9% in men, with a female-to-male ratio close to 3:1 that becomes evident
79 shortly after menarche [1,3,4]. Beyond frequency, migraine in women tends to manifest with longer
80 attack duration, greater severity, more pronounced allodynia and photophobia, and higher likelihood
81 of chronification, particularly around menstruation [3,8,17]. These clinical features translate into higher
82 interictal disability, greater absenteeism and presenteeism, and a disproportionate contribution to the
83 global disability footprint attributable to headache disorders [1,4,17].

84 Migraine is no longer conceptualized as a purely episodic benign headache. It is now recognized
85 as a systemic condition intersecting cardiovascular, metabolic and mental health [4,18,19]. In women,
86 it clusters with endothelial dysfunction, hypertension, depression and anxiety disorders, and aura is an
87 independent risk factor for ischemic stroke, especially in the presence of combined hormonal
88 contraception and smoking [18]. This matters for exercise prescription: interventions that
89 simultaneously address migraine, cardiovascular risk and affective comorbidity are mechanistically
90 attractive, and RT meets several of these criteria.

91 **THE FEMALE HORMONAL AXIS IN MIGRAINE PATHOPHYSIOLOGY**

92 **Estrogen withdrawal and the vulnerability window**

93 The “estrogen withdrawal hypothesis” posits that a rapid fall in plasma estradiol during the late
94 luteal phase is a key proximate trigger of menstrual and menstrually related migraine [8,9,20].
95 Empirical support is substantial. Premenstrual administration of estradiol delays, attenuates or
96 prevents perimenstrual attacks in controlled studies; conversely, artificially inducing estrogen
97 withdrawal provokes attacks in susceptible women [9,20]. The clinical entities of pure menstrual
98 migraine (PMM) and menstrually related migraine (MRM), defined by the International Headache
99 Society (IHS) in the International Classification of Headache Disorders, 3rd edition (ICHD-3) and
100 operationalized in its Appendix, capture this temporal clustering and identify a phenotype in which

101 attacks are typically longer, more intense and less responsive to acute treatment than non- menstrual
102 attacks [8,9].

103 Mechanistically, rapid estradiol withdrawal appears to destabilize several interdependent systems
104 simultaneously. It modulates hypothalamic corticotropin-releasing hormone tone, shifts opioidergic
105 and serotonergic signaling, alters nitric oxide and prostaglandin production in cerebral and meningeal
106 vasculature, and, crucially, changes the excitability of trigeminovascular afferents and their
107 neuropeptide output [10,12,20]. Thus, the late luteal phase constitutes a multi-system “vulnerability
108 window” rather than a purely hormonal event, and this window is reflected in clinical and
109 neurophysiological observations in several human studies [10,12,17]. Autonomic involvement is
110 discussed below in relation to heart-rate variability (HRV), vagal modulation and baroreflex-related
111 regulation.

112 **Estrogen receptor distribution and trigeminovascular sensitization**

113 Estrogen exerts its effects through three principal receptors: estrogen receptor alpha (ER α), estrogen
114 receptor beta (ER β) and the G-protein-coupled estrogen receptor (GPER). These are expressed across migraine-
115 relevant structures, including trigeminal ganglion neurons, meningeal afferents, dural vasculature, endothelial
116 cells and the trigeminocervical complex [2,10,12]. Receptor-specific signaling modulates neuronal excitability,
117 neuropeptide synthesis and the responsiveness of ion channels implicated in migraine, among them transient
118 receptor potential ankyrin 1 (TRPA1), transient receptor potential vanilloid 1 (TRPV1) and transient receptor
119 potential melastatin 3 (TRPM3), the latter recently proposed as a sex-related target in migraine in females
120 [12,13]. Rapid non-genomic actions via GPER can further tune vascular reactivity and nociceptor thresholds on
121 a timescale compatible with ictal dynamics [10,12].

122 **The estrogen-CGRP interface**

123 CGRP is the archetypal migraine neuropeptide, released from activated trigeminal and meningeal
124 afferents, producing meningeal vasodilation, mast cell degranulation, neurogenic inflammation and
125 sensitization of second-order neurons in the trigeminal nucleus caudalis [5,11,21]. Women exhibit
126 higher circulating CGRP concentrations and greater trigeminovascular responsiveness to CGRP than

men, and these differences are modulated by the menstrual cycle, pregnancy and menopause [2,11,21]. The canonical calcitonin gene-related peptide (CGRP) receptor complex, composed of the calcitonin-receptor-like receptor (CLR), receptor activity-modifying protein 1 (RAMP1) and receptor component protein (RCP), shows sex- and hormone-dependent differences in expression and signaling efficiency, potentially explaining the greater female sensitivity of the pathway [11,21].

This estrogen-CGRP coupling has direct clinical relevance. Real-world data indicate that anti-CGRP monoclonal antibodies are effective in menstrually related migraine, with reductions in headache days that are at least comparable to those observed in non-menstrual migraine [22]. It also sets the stage for non-pharmacological interventions. Any strategy that stabilizes autonomic, vascular and nociceptive tone during the estrogen-withdrawal window may dampen the downstream CGRP-driven cascade, even without directly blocking the peptide.

Additional neuroendocrine players (e.g., prolactin as a pronociceptive modulator and oxytocin as an antinociceptive hormone) further enrich the hormonal landscape of migraine in females and provide biologically plausible links between stress, lactation, sleep and attack susceptibility [23]. These pathways are beyond the primary focus of this review but reinforce the notion that migraine in females cannot be understood without an integrative neuroendocrine perspective (**Figure 1**).

INSERT FIGURE 1 HERE

Figure 1. Female reproductive life course, estradiol dynamics and migraine vulnerability. (A) Schematic representation of the female reproductive life course, highlighting major phases in estradiol exposure and relative migraine prevalence in females. Estradiol levels are low during childhood, become cyclical after menarche, fluctuate across the reproductive years, rise during pregnancy, fall abruptly postpartum, become erratic during perimenopause and remain low after menopause. The upper curve is schematic and represents relative migraine prevalence across reproductive phases rather than quantitative estradiol concentrations. (B) Estradiol may influence migraine-relevant biology through estrogen receptors, including $ER\alpha$, $ER\beta$ and GPER, expressed across trigeminovascular, vascular/endothelial and central modulatory tissues. These pathways may interact with calcitonin gene-related peptide (CGRP) signaling and trigeminovascular responsiveness. (C) Estradiol fluctuation or withdrawal is presented as a vulnerability window during which trigeminovascular excitability and CGRP responsiveness may increase, potentially lowering the migraine attack threshold. Numbers indicate: 1, estradiol fluctuation or withdrawal; 2, estrogen receptor signaling; 3, trigeminovascular/CGRP pathway responsiveness; 4, neurogenic inflammatory and vascular/endothelial modulation; and 5, potential attack-threshold reduction with higher attack susceptibility. This model is conceptual and does not imply that hormonal variation alone explains migraine in all females.

158 **WHY CONSIDER RESISTANCE TRAINING? PHYSIOLOGICAL RATIONALE**

159 Exercise modifies virtually every physiological axis implicated in migraine pathophysiology: autonomic
160 balance, endothelial and cerebrovascular function, systemic low-grade inflammation, skeletal muscle secretory
161 activity, endogenous opioid and endocannabinoid tone, and central pain modulation [24–27]. Historically,
162 aerobic exercise has dominated migraine research, partly due to safety concerns surrounding exertional
163 headache and partly by analogy with cardiovascular prevention [14,28]. RT has long been viewed with caution
164 because heavy lifting, breath-holding and Valsalva-like maneuvers can transiently increase blood pressure and
165 cerebrovascular transmural pressure [43]. However, available supervised and progressive RT trials have not
166 reported an increase in migraine frequency.

167 Several features make RT particularly attractive for women with migraine. Unlike prolonged aerobic
168 sessions, RT can be structured in short, discrete units compatible with busy life-stages; nevertheless, supervised
169 RT may also create financial and access barriers for patients with fewer resources. It preserves lean mass and
170 bone mineral density, which are clinically relevant across the perimenopausal transition; it improves insulin
171 sensitivity and body composition, ameliorating comorbidities that aggravate migraine burden; and it engages the
172 neuromuscular system in ways that are distinct from, and complementary to, aerobic conditioning [25,29,30].
173 These practical advantages coexist with a mechanistic rationale, explored in the following sections.

174 **CANDIDATE MECHANISMS LINKING RESISTANCE TRAINING TO MIGRAINE BIOLOGY**

175 **Autonomic regulation and baroreflex function**

176 Migraine is characterized by an interictal shift toward sympathetic predominance and reduced
177 vagal modulation, captured by lower time- and frequency-domain indices of heart rate variability
178 (HRV) [17,19]. This autonomic imbalance aligns with the hyperresponsive trigeminovascular system
179 and with the reduced resilience observed in the late luteal phase. Re-establishing autonomic tone is
180 therefore a biologically sensible therapeutic target.

181 Acute RT elicits transient sympathetic activation and post-exercise parasympathetic reactivation that are
182 dose-dependent on load, training volume (the total amount of work, commonly expressed as sets $\times$ repetitions $\times$
183 load) and rest intervals [31,32]. Chronic, progressive RT, particularly when incorporating moderate loads and

184 sufficient recovery, is associated with improved resting HRV, enhanced baroreflex sensitivity and reduced blood
185 pressure reactivity to stress in non-migraine populations [31,32]. Although direct HRV data in women with
186 migraine undergoing RT remain very limited, the convergence of these adaptations with the autonomic biology
187 of migraine provides a coherent a priori rationale for sustained, supervised programmes rather than intermittent
188 high-intensity exposures.

189 **Neurovascular and endothelial function**

190 Endothelial dysfunction, arterial stiffness and altered cerebrovascular reactivity are observed in
191 women with migraine, particularly those with aura, and contribute both to symptom generation and to
192 the associated cerebrovascular risk [18]. Nitric-oxide bioavailability, endothelium- dependent
193 vasodilation and pulse-wave velocity are central biomarkers in this domain.

194 The effects of RT on vascular function are nuanced. Acute heavy-load sessions transiently increase arterial
195 stiffness, whereas long-term, moderate-intensity RT (especially when combined with aerobic exercise) improves
196 flow-mediated dilation, reduces carotid-femoral pulse-wave velocity and supports favourable remodelling of
197 peripheral arteries [29,30,33,34]. Importantly, available vascular evidence suggests that RT may induce sex-
198 dependent adaptations in arterial function and stiffness, but current data do not establish that women derive
199 greater endothelial benefits than men. Whether endothelial responses to RT differ by sex, and how these
200 responses are modified by estrogen status, remains insufficiently characterized [30]. These adaptations are
201 mechanistically aligned with stabilization of the migraine-vulnerable cerebrovascular milieu and may reduce the
202 vascular context that facilitates CGRP-mediated meningeal vasodilation.

203 **Systemic and neurogenic inflammation**

204 Migraine involves both central neurogenic inflammation-mediated by substance P, neurokinin A and CGRP
205 and a low-grade systemic inflammatory state that predicts chronification [4,5,18]. RT consistently reduces
206 chronic inflammatory markers such as C-reactive protein, IL-6 (in its chronically elevated form) and TNF- α ,
207 while enhancing anti-inflammatory myokine signaling [26,35]. Skeletal muscle, now conceptualized as a
208 secretory organ, releases myokines (cytokines and peptides produced or released by contracting skeletal muscle)
209 and exerkines (exercise-induced circulating signaling molecules), including cytokines, neurotrophins and

210 peptide mediators, that may influence immune cell phenotype, endothelial function and central nociception
211 [26,35]. While no intervention has directly demonstrated that RT-induced changes in myokines reduce migraine
212 attacks, the biological overlap between exerkin targets and migraine-relevant substrates is sufficient to warrant
213 focused mechanistic trials.

214 **Endogenous pain modulation and exercise-induced hypoalgesia**

215 A robust body of work documents exercise-induced hypoalgesia (EIH) (i.e., the transient
216 reduction in pain perception after acute exercise) and, with repeated training, sustained improvements
217 in conditioned pain modulation and descending inhibitory function [24,36,37]. Mechanisms include
218 engagement of endogenous opioid and endocannabinoid systems, activation of the
219 rostroventromedial medulla and periaqueductal grey, and modulation of spinal and trigeminal
220 nociceptive gain [24,36,37]. RT specifically produces reliable EIH responses when performed at
221 moderate-to-high intensity with adequate volume, and these responses appear relatively preserved in
222 individuals with chronic pain when load progression is individualized [24,36]. In migraine, where
223 descending inhibitory function is impaired and central sensitization frequent, this domain constitutes
224 perhaps the most direct mechanistic link between RT and symptomatic benefit.

225 **Sleep, mood and behavioural co-regulation**

226 Sleep disturbance, depression and anxiety substantially overlap with migraine, and the relationships are
227 bidirectional rather than simply causal in one direction [17,38]. Sleep disruption can precipitate attacks,
228 recurrent attacks can worsen sleep and internalizing symptoms, and anxiety/depression may amplify migraine-
229 related disability. RT may improve sleep architecture and self-reported sleep quality, as well as depressive and
230 anxiety symptoms [29]. Some of the migraine-related benefit of exercise may therefore be mediated indirectly
231 through improved sleep and mood, with downstream effects on autonomic and nociceptive networks (Figure 2).

232 **INSERT FIGURE 2 HERE**

233 **Figure 2.** Candidate biological pathways through which progressive resistance training engages migraine-
234 relevant physiology in females. Resistance training may influence migraine-relevant physiology through four
235 partially overlapping pathways: autonomic regulation, neurovascular and endothelial function, inflammatory and
236 immune signaling, and endogenous pain modulation. Repeated training may support improved heart rate

237 variability, vagal modulation, baroreflex-related regulation, endothelial function, nitric oxide bioavailability,
238 vascular tone regulation, inflammatory control and descending pain inhibition. Vagal modulation and baroreflex-
239 related regulation are typically indexed by heart rate variability and baroreflex sensitivity measures. Demanding
240 sessions (here, high-load or high-effort training with short recovery, or sessions performed with dehydration,
241 hypoglycaemia or breath-holding) may transiently increase sympathetic predominance during immediate
242 recovery (the minutes-to-hours period after exercise), highlighting the importance of individualized dosing. The
243 proposed integrated implication is improved physiological buffering capacity, potentially lower migraine
244 vulnerability and a higher attack threshold. This model is hypothesis-generating and should not be interpreted as
245 direct CGRP blockade or as a substitute for individualized pharmacological preventive treatment.

246 **CLINICAL EVIDENCE FOR RESISTANCE TRAINING IN MIGRAINE**

247 Clinical evidence specifically supporting RT in migraine has grown substantially since approximately
248 2018. Randomized controlled trials of neck-specific strengthening demonstrate reductions in headache
249 frequency and neck-related disability, particularly in women with migraine and comorbid cervicogenic features
250 [39]. Pragmatic programmes combining resistance and aerobic training report reductions in monthly migraine
251 days comparable to or exceeding those of pharmacological preventive treatment [15,16].

252 Two recent syntheses are particularly informative. In the network meta-analysis by
253 Woldeamanuel and Oliveira, encompassing 21 trials and 1,195 patients (female-to-male ratio ≈ 6.7),
254 strength/resistance training produced the largest reduction in monthly migraine frequency
255 (mean difference -3.55 monthly migraine days, 95% CI -6.15 to -0.95), outperforming high-intensity aerobic
256 exercise (-3.13), moderate-intensity aerobic exercise (-2.18) and topiramate (-0.98) [16]. In the multilevel
257 network meta-analysis by Xie and colleagues (27 randomized controlled trials [RCTs], 1,611 participants),
258 combined aerobic plus resistance exercise ranked first (standardized mean differences [SMD] = -1.85 ; Surface
259 Under the Cumulative Ranking curve [SUCRA] = 0.91), followed by resistance exercise alone (SMD = -1.45 ;
260 SUCRA = 0.81), with an identified optimal window of 300-600 metabolic equivalent task (MET)-min/week at
261 4.5-5.5 METs over 8-10 weeks [15]. Complementary dose-response analyses for aerobic exercise estimate a
262 minimum effective dose around 200-300 cumulative minutes, with maximal benefit approaching 900-950
263 minutes across an intervention [14]. These estimates should be interpreted cautiously because the certainty of
264 evidence was rated as low to very low by the source authors. For comparisons in which the 95% confidence
265 interval excluded the null value, we report this directly rather than adding p values that were not provided in the
266 original manuscript. Despite these limitations, independent syntheses appear to converge on a favorable signal

for resistance training, although this signal remains preliminary and should not be interpreted as guideline-level evidence (Table 1).

[Table 1 near here]

Several caveats merit explicit acknowledgement. First, the trials underpinning these syntheses are small, heterogeneous in training parameters and rarely stratify by sex or menstrual phase. Second, adherence to RT protocols in community settings is a known challenge, and supervision appears to amplify effects [40,41]. Third, the distinction between chronic and episodic migraine phenotypes, and between menstrual and non-menstrual attacks, is blurred in many studies, limiting inference for sex-specific subgroups.

AN INTEGRATIVE ATTACK-THRESHOLD MODEL OF RESISTANCE TRAINING FOR MIGRAINE IN FEMALES

Consistent with migraine threshold and sensory-processing models, attack generation can be viewed as a dynamic balance between destabilizing inputs and stabilizing physiological buffers. In this framework, the probability that a migraine-susceptible brain generates a full attack increases when factors such as estrogen withdrawal, cortical hyperexcitability, autonomic instability, inflammation, poor sleep or stress outweigh stabilizing influences such as autonomic resilience, intact descending inhibition, vascular homeostasis and low inflammatory tone [42]. In women, the late luteal phase may transiently shift this balance toward vulnerability.

Chronic, progressively dosed RT plausibly shifts the balance toward stability along four interlocking axes: (i) enhancing vagal tone and baroreflex function to damp autonomic oscillations around the hormonal withdrawal window; (ii) improving endothelial function and reducing arterial stiffness, thereby narrowing the vascular context that may facilitate CGRP-driven meningeal vasodilation; (iii) lowering systemic and neurogenic inflammatory priming through myokine-mediated anti-inflammatory effects; and (iv) restoring descending pain inhibition and reducing central sensitization via EIH pathways (Table 2).

293 *A fifth, indirect pathway — improved sleep architecture and reduced depressive and anxiety symptoms — may further modulate autonomic and*
294 *nociceptive networks [17,29,38]. All mechanisms are hypothesis-generating and are best interpreted as convergent contributors to physiological buffering*
295 *capacity rather than direct antagonism of the estrogen–CGRP axis. CGRP, calcitonin gene-related peptide; HRV, heart-rate variability; IL-6, interleukin-*
296 *6; RT, resistance training; TNF- α , tumor necrosis factor alpha.*

297 Taken together, these pathways support a conceptual attack-threshold model in which RT is not
298 expected to act through a single migraine-specific mechanism, but rather through convergent
299 adaptations that may increase physiological buffering capacity. In this model, autonomic regulation,
300 neurovascular and endothelial function, inflammatory/immune tone and endogenous pain modulation
301 interact with the hormonal context of females to influence vulnerability to attack initiation. Poorly
302 titrated or unusually strenuous sessions may transiently increase sympathetic stress, whereas
303 appropriately progressed RT may, over time, shift the system toward a less vulnerable physiological
304 state (**Figure 3**).

305 Acute poorly individualized sessions (i.e., excessive load, insufficient recovery, dehydration or
306 hypoglycaemia) can, paradoxically, act as physiological stressors, underscoring the importance of
307 individualized progression. Critically, these adaptations do not antagonize the estrogen-CGRP axis
308 directly and are therefore best conceptualized as adjunctive, strengthening physiological buffers that
309 complement CGRP-targeted therapy rather than replacing it. This framing reconciles the apparent
310 paradox between the empirical effect sizes of RT on migraine frequency and the molecular specificity
311 of modern CGRP-targeting agents.

312 INSERT FIGURE 3 HERE

313 Figure 3. Integrative attack-threshold model linking resistance training adaptations to migraine vulnerability in
314 females. The figure presents a hypothesized model in which resistance training (RT) may influence migraine
315 vulnerability through convergent effects on autonomic regulation, neurovascular function,
316 inflammatory/immune tone and endogenous pain modulation. These adaptations are shown as interacting with
317 the hormonal context of females, including late-luteal estradiol withdrawal, altered estrogen receptor signaling
318 and greater CGRP-pathway responsiveness. The central balance represents the proposed migraine attack
319 threshold, whereby poorly titrated or unusually strenuous sessions may transiently increase sympathetic stress,
320 whereas appropriately progressed RT may support greater physiological buffering capacity and a less vulnerable
321 state over time. The model is conceptual and hypothesis-generating and should not be interpreted as evidence

322 that RT directly reduces migraine burden in all females or replaces individualized pharmacological preventive
323 treatment.

324 **TRANSLATIONAL PRESCRIPTION: PRINCIPLES FOR WOMEN WITH MIGRAINE**

325 Translating the above mechanisms into prescription requires attention to sex-, phenotype- and
326 life-stage-specific nuances, particularly because migraine expression and vulnerability may vary
327 across the menstrual cycle, pregnancy, postpartum and the perimenopausal transition [8,9,17,19,20].
328 Based on the available migraine exercise evidence and broadly accepted resistance-training
329 principles [15,16,25], we propose the following operational principles, while noting that phase-specific
330 RT prescriptions for menstruation, pregnancy, postpartum and menopause have not yet been tested
331 directly in migraine trials.

332 Programming should be progressive, supervised where possible, and emphasize moderate loads (60-80% 1-
333 repetition maximum [RM]) across 6-10 compound exercises, with 2-3 sessions per week, aligning weekly
334 volume to the 300-600 MET-min/week window identified as effective [15,16]. Compound exercises may
335 include squat or leg-press variants, hip-hinge/deadlift variants, horizontal or vertical pulling exercises, pushing
336 exercises and loaded carries or trunk-stability movements, selected according to symptoms, experience and
337 access to equipment [25]. Neck-specific strengthening should be considered when cervical dysfunction is
338 present, as it adds targeted benefit with minimal incremental risk [39]. Heavy, near-maximal efforts involving
339 breath-holding or pronounced Valsalva manoeuvres should be progressed cautiously, particularly in patients
340 with uncontrolled blood pressure, because these manoeuvres can produce acute haemodynamic and
341 cerebrovascular fluctuations [43]. Patients with a history of exertion-triggered headache should not be
342 automatically excluded from RT; rather, they warrant additional caution because physical exertion and Valsalva-
343 like manoeuvres are recognized precipitants of exertional headache syndromes [44]. Practical safeguards include
344 medical screening when clinically indicated, avoidance of breath-holding, longer rest intervals, conservative
345 load progression, hydration, avoidance of hypoglycaemia and discontinuation of a session if a new, abrupt or
346 atypical headache occurs.

347 Menstrual-cycle- and reproductive-phase-informed prescription is biologically plausible but not yet
348 evidence-based, because migraine vulnerability varies across the menstrual cycle and reproductive lifespan, and

estradiol withdrawal may define a transient vulnerability window [8,9,17,20,45]. However, no trials have directly tested phase-specific RT programming in menstruating, pregnant, postpartum, perimenopausal or postmenopausal women with migraine. Accordingly, cycle-based adjustments should be considered symptom-guided theoretical extrapolations rather than standardized rules: RT may be maintained during vulnerable phases through autoregulated reductions in load, volume or proximity to failure [25], whereas higher-load sessions should be scheduled according to individual tolerance rather than cycle phase alone. In practice, this means reducing load, total sets or effort during days with premonitory symptoms, poor sleep, dehydration, heavy menstrual symptoms or heightened attack susceptibility, and progressing again when symptoms stabilize. Perimenopause and menopause warrant particular attention: the combination of hormonal instability and rising cardiovascular risk makes RT potentially valuable, with likely synergistic benefits for bone, metabolic, cardiovascular and mood outcomes [9,19,29,30,45].

Adherence and behavioural support are likely to be important for implementation, although direct evidence that digital or community-based support improves adherence to RT in women with migraine remains limited. Regular physical exercise may have a preventive role in migraine, but the optimal frequency, intensity and delivery format remain uncertain [38]. In a supervised aerobic exercise trial in patients with migraine and co-existing tension-type headache and neck pain, exercise improved physical fitness, physical activity and migraine burden, with within-group reductions in migraine frequency, intensity and duration [40]. These findings support the pragmatic use of supervised, symptom-guided and educational strategies to facilitate participation, while highlighting the need to test adherence-enhancing approaches directly in RT trials. Integration with pharmacological preventive treatment, including anti-CGRP agents, should therefore be regarded as complementary rather than competitive.

RESEARCH GAPS AND FUTURE DIRECTIONS

Several limitations of this review should be acknowledged before outlining future research priorities. First, this is a narrative, mechanistically oriented review rather than a systematic review or meta-analysis. Although it integrates clinical, hormonal and physiological evidence, its design carries

375 an inherent risk of citation selectivity and does not allow formal quantification of effect sizes, certainty
376 of evidence or publication bias. Second, the proposed female-specific framework is constrained by the
377 available primary literature. Most exercise trials in migraine include predominantly, but not exclusively,
378 women, and few report sex-disaggregated outcomes. Moreover, no RT trial to date has been
379 specifically powered to test sex as an effect modifier or to examine moderation by menstrual-cycle
380 phase, hormonal contraceptive use, perimenopause or menopause. Therefore, the mechanistic model
381 advanced here should be interpreted as biologically plausible and hypothesis-generating rather than
382 as definitive evidence of female- specific efficacy.

383 Current evidence nevertheless supports a potentially meaningful effect of RT on migraine burden,
384 but several critical gaps remain before RT can be firmly incorporated into sex-informed clinical
385 guidelines. Most existing trials are small, unblinded with respect to clinician assessment, and
386 underpowered for subgroup analyses by sex, phenotype or menstrual-cycle phase. Direct mechanistic
387 endpoints—including interictal CGRP, HRV, pulse-wave velocity, endothelial function and conditioned
388 pain modulation—are rarely embedded in migraine exercise trials, limiting our ability to link biology to
389 outcomes. The heterogeneity of training parameters prevents fine-grained dose–response inference
390 for RT specifically, and long-term follow-up beyond 12 weeks is limited.

391 Priority avenues include: (i) adequately powered RCTs of supervised, progressive RT in women with
392 menstrually related migraine, stratified by cycle phase and incorporating interictal CGRP, HRV and endothelial
393 function as mechanistic secondary outcomes; (ii) factorial trials combining RT with pharmacological preventive
394 treatment, including anti-CGRP monoclonal antibodies and gepants, to test additivity or synergy; (iii)
395 perimenopause- and menopause-specific interventions integrating RT, cardiovascular prevention and mood
396 outcomes; and (iv) implementation studies testing telecoaching, supervised group formats and behavioural
397 support for adherence. Standardization of reporting using the Consensus on Exercise Reporting Template
398 (CERT) or the Template for Intervention Description and Replication (TIDieR), together with pre-registration,
399 will be essential to raise the certainty of evidence from its current low-to-very-low status.

400 CONCLUSION

401 Migraine in females is a hormonally influenced, neuroendocrine, neurovascular and nociceptive disorder
402 whose biology may be amenable to systemic physiological stabilization. Resistance training, long overshadowed
403 by aerobic exercise in the migraine literature, now emerges from independent network meta-analyses as a
404 leading non-pharmacological modality for reducing attack frequency. Its effects plausibly act through
405 autonomic, endothelial, inflammatory and pain-modulatory mechanisms that overlap meaningfully with the
406 estrogen-CGRP substrate of migraine in females. Although the evidence base is still heterogeneous, the
407 convergence of mechanistic rationale and clinical signal justifies its deliberate inclusion in individualized, sex-
408 informed treatment plans, as an adjunct to, rather than a substitute for, contemporary pharmacotherapy. Future
409 trials must embed direct mechanistic readouts and explicit sex-specific stratification so that the promise of RT in
410 women with migraine can be evaluated with sufficient precision to inform future guideline recommendations,
411 which would likely remain conditional until higher-certainty evidence becomes available.

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Figure 1

Female reproductive life course, estradiol dynamics and migraine vulnerability

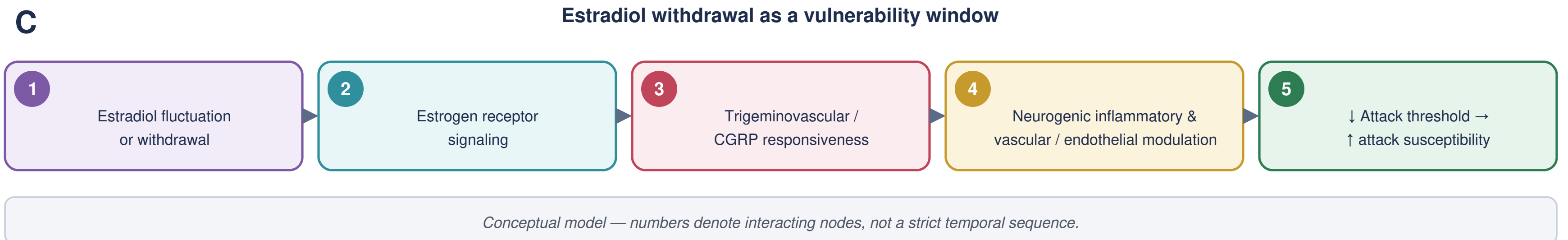
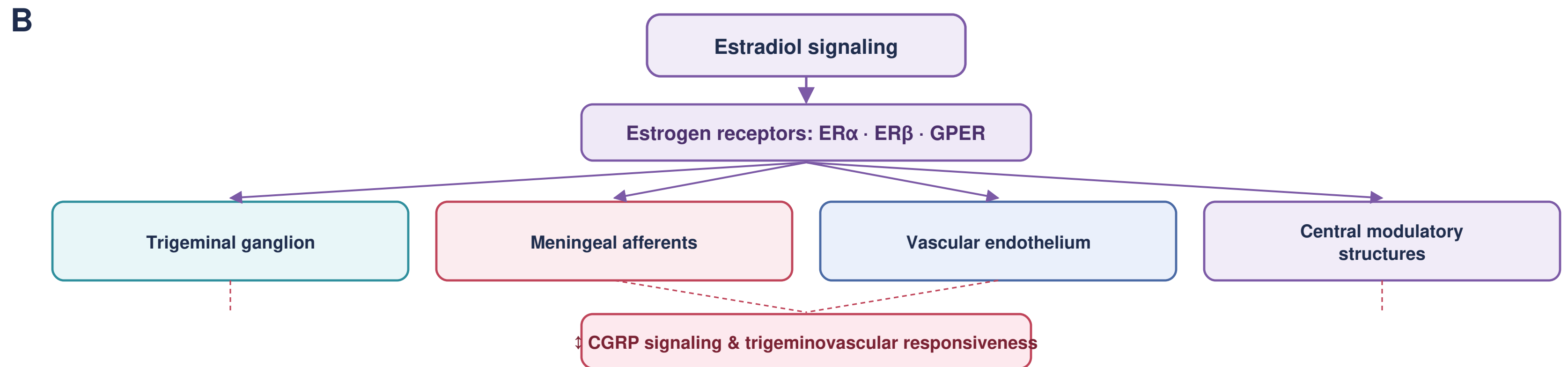
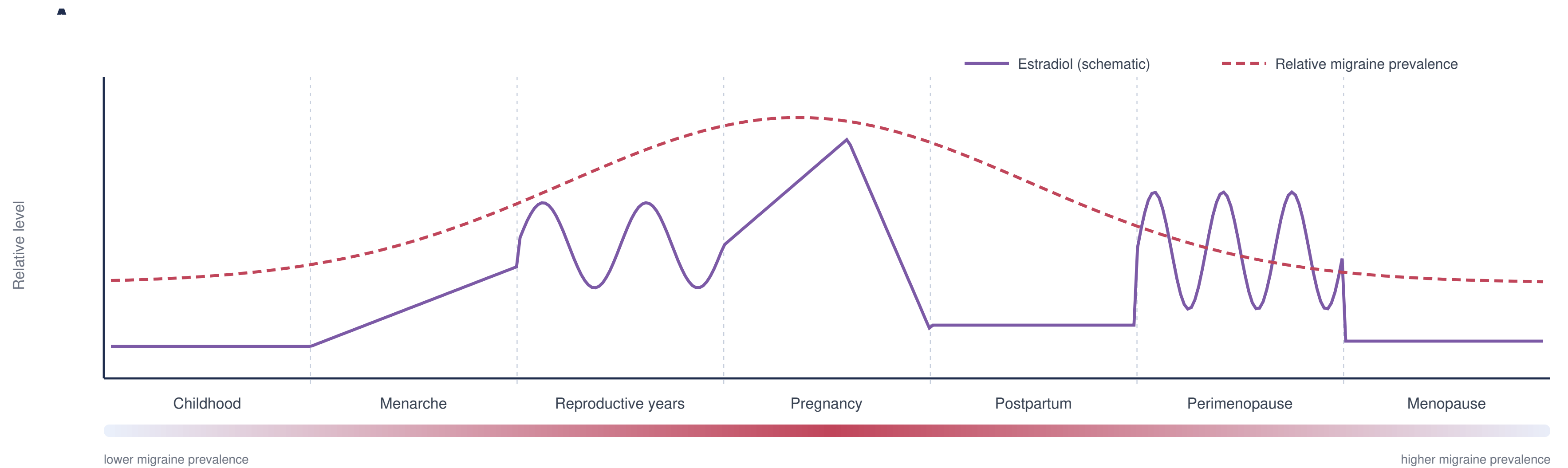


Figure 2

Candidate biological pathways through which progressive resistance training engages migraine-relevant physiology in females

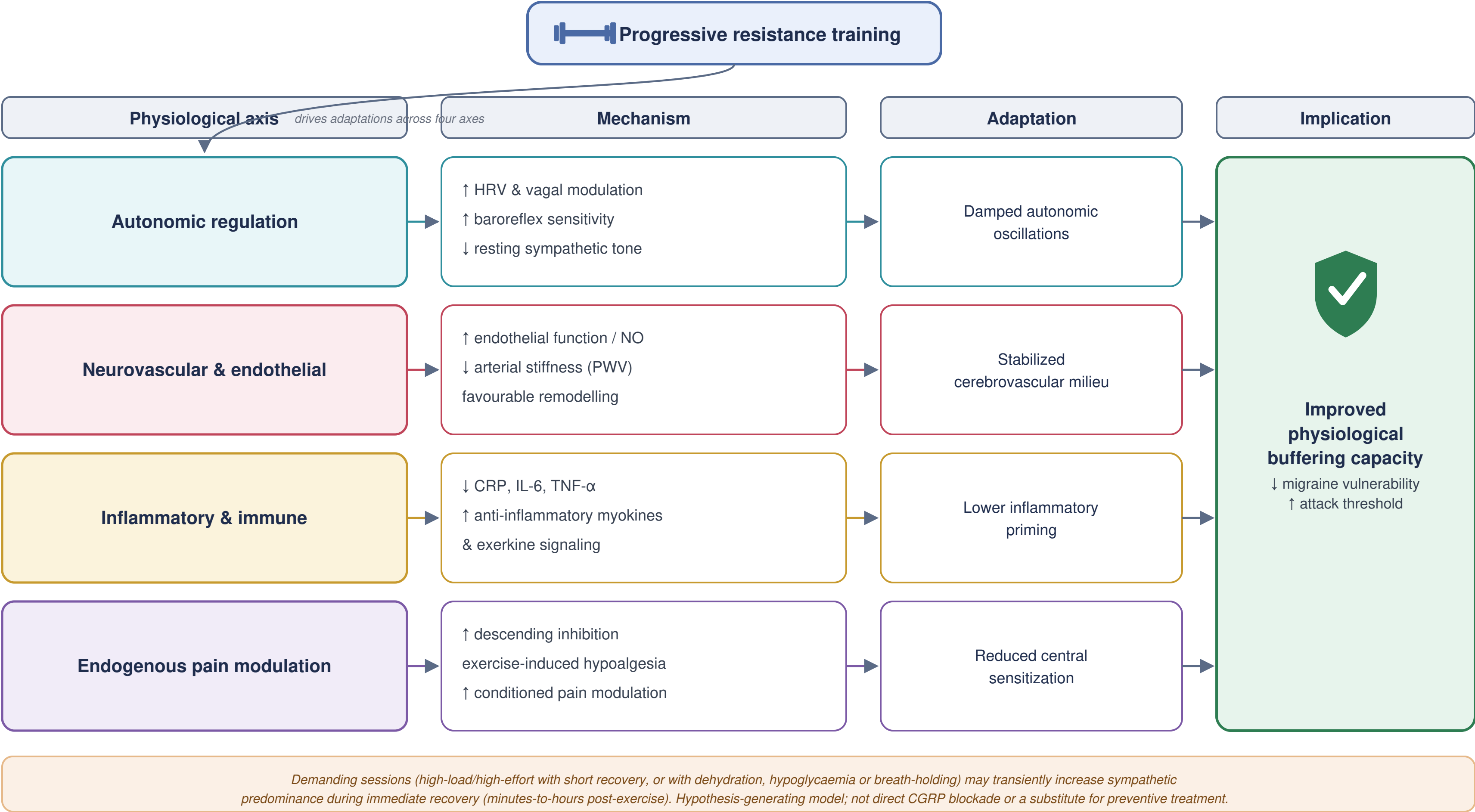
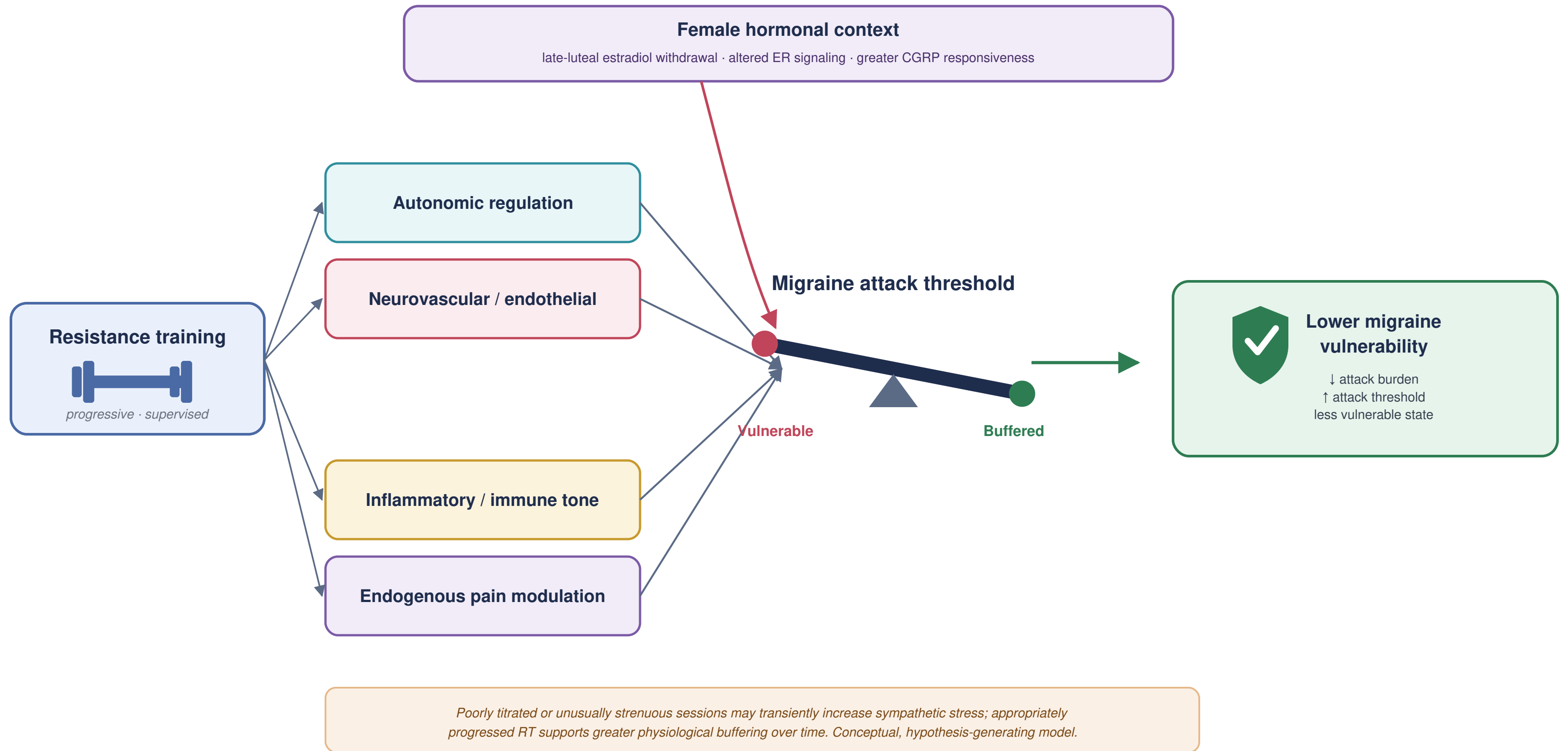


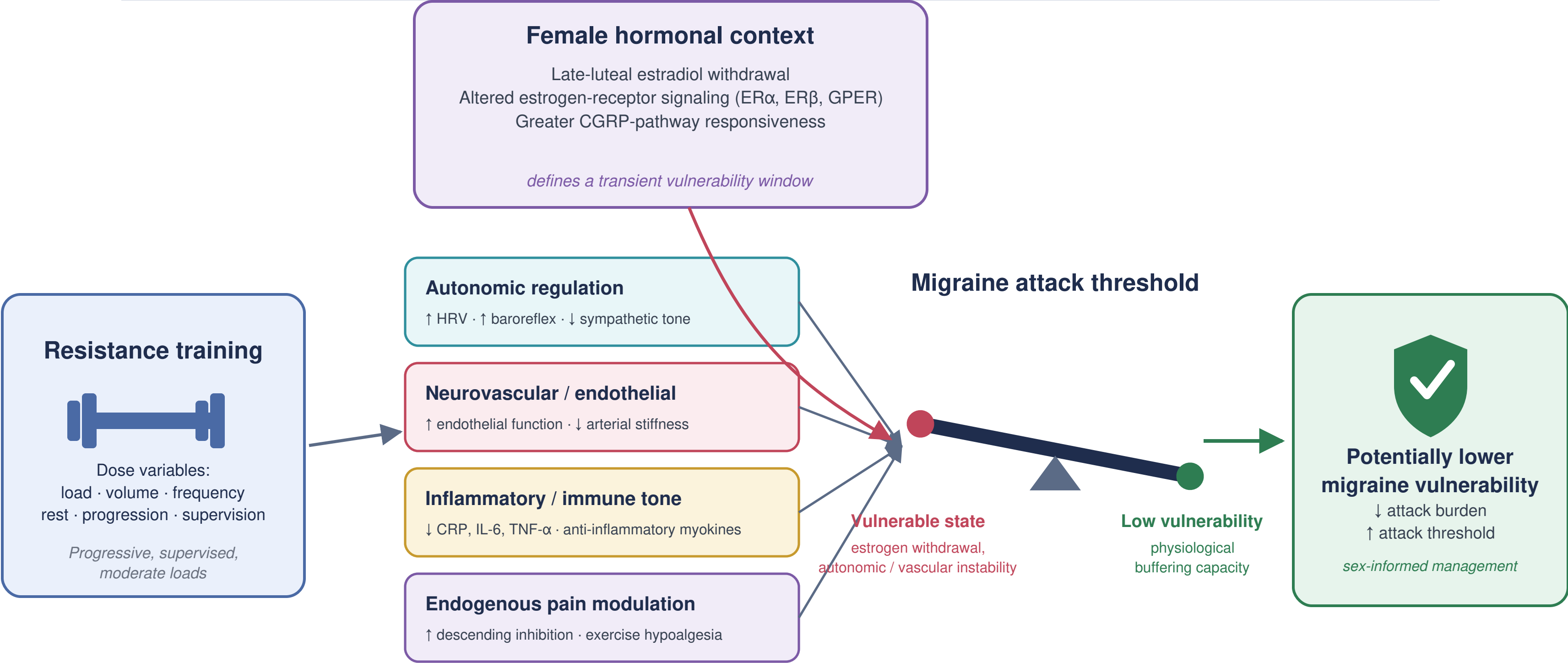
Figure 3

Integrative attack-threshold model linking resistance training adaptations to migraine vulnerability in females



Resistance Training and Migraine Vulnerability in Females

A sex-informed, mechanistic attack-threshold framework



Conceptual, hypothesis-generating model.

Resistance training is proposed as an adjunct that strengthens physiological buffers — not a direct CGRP blocker or a replacement for pharmacological preventive treatment.

1 **Table 1. Summary of clinical evidence for resistance and strength training in migraine.**

Study (year) [ref]	Design; sample (F:M)	Intervention	Comparator(s)	Primary outcome	Key finding for resistance training
Woldeamanuel & Oliveira, 2022 [16]	Systematic review + network meta-analysis; 21 trials, 1,195 patients (F:M $\approx$ 6.7:1)	Strength / resistance training	High-intensity aerobic; moderate-intensity aerobic; topiramate	Reduction in monthly migraine frequency (days/month)	Strength / resistance training produced the largest reduction, outperforming high-intensity aerobic (-3.13), moderate-intensity aerobic (-2.18) and topiramate (-0.98 days/month)
Xie et al. [15]	Multilevel network meta-analysis; 27 RCTs, 1,611 participants	Combined aerobic + resistance; resistance training alone	Other exercise modalities within the network	Reduction in monthly migraine days (SMD; SUCRA ranking)	Combined aerobic + resistance ranked first (SMD = -1.85 ; SUCRA = 0.91); resistance alone second (SMD = -1.45 ; SUCRA = 0.81); optimal dose 300–600 MET-min/week at 4.5–5.5 METs over 8–10 weeks
Luedtke et al., 2020 [39]	Randomized controlled trial	Neck-specific strengthening exercise	Control / usual care	Headache frequency; neck-related disability	Reduced migraine frequency and neck-related disability, particularly in women with comorbid cervicogenic features
Kröll et al., 2018 [40]	Randomized controlled trial	Supervised aerobic exercise (migraine with co-existing tension-type headache and neck pain)	Usual care	Physical fitness; physical activity; migraine burden	Improved fitness and physical activity, with within-group reductions in migraine frequency, intensity and duration
Ogrezeanu et al., 2025 [14]	Systematic review + dose-response meta-analysis (aerobic)	Aerobic exercise (dose-response)	—	Migraine frequency (cumulative dose)	Minimum effective dose $\approx$ 200–300 cumulative minutes; maximal benefit approaching $\approx$ 900–950 minutes across an intervention

2 Values in parentheses are between-group mean reductions in monthly migraine days versus the referenced comparator unless otherwise stated. Aerobic-
3 only syntheses (refs [14,40]) are included to provide dose-response and supervised-exercise context. The certainty of evidence across these syntheses was
4 rated low to very low by the original authors. F:M, female-to-male ratio; MET, metabolic equivalent of task; RCT, randomized controlled trial; SMD,
5 standardized mean difference; SUCRA, surface under the cumulative ranking curve.

1 **Table 2. Candidate mechanisms linking progressive resistance training to migraine-relevant physiology in women.**

Mechanistic axis	Migraine-related abnormality	Adaptation to progressive resistance training	Representative measures / biomarkers	Proposed relevance to the migraine attack threshold	Evidence status [ref]
Autonomic regulation and baroreflex function	Interictal sympathetic predominance and reduced vagal modulation (lower heart-rate variability)	Improved resting heart-rate variability, enhanced baroreflex sensitivity and reduced blood-pressure reactivity to stress	Time- and frequency-domain HRV; baroreflex sensitivity	Damps autonomic oscillations around the estrogen-withdrawal window	Indirect: adaptations shown in non-migraine populations; no direct HRV data in women with migraine undergoing RT [17,19,31,32]
Neurovascular and endothelial function	Endothelial dysfunction, arterial stiffness and altered cerebrovascular reactivity (notably with aura)	Improved flow-mediated dilation, reduced carotid-femoral pulse-wave velocity and favourable arterial remodelling (moderate-intensity, long-term, especially combined with aerobic exercise)	Flow-mediated dilation; nitric-oxide bioavailability; pulse-wave velocity	Narrows the vascular context that may facilitate CGRP-driven meningeal vasodilation	Mechanistically aligned; sex- and estrogen-related modification insufficiently characterized [18,29,30,33,34]
Systemic and neurogenic inflammation	Neurogenic inflammation (substance P, neurokinin A, CGRP) and a low-grade systemic inflammatory state predicting chronification	Reduced C-reactive protein and chronically elevated IL-6 and TNF- α ; enhanced anti-inflammatory myokine / exerkine signaling	C-reactive protein; IL-6; TNF- α ; myokines / exerkines	Lowers systemic and neurogenic inflammatory priming	Biological overlap established; no trial has directly linked RT-induced myokine change to migraine reduction [4,5,18,26,35]
Endogenous pain modulation (exercise-induced hypoalgesia)	Impaired descending inhibition and frequent central sensitization	Reliable exercise-induced hypoalgesia and improved conditioned pain modulation; engagement of endogenous opioid and endocannabinoid systems, periaqueductal grey and rostroventromedial medulla	Conditioned pain modulation; pressure / pain thresholds	Restores descending inhibition and reduces central sensitization — the most direct mechanistic link	Robust in pain-free and chronic-pain populations; migraine-specific RT data limited [24,36,37]