

Longer Walking Duration Protects Against Cognitive Decline In Preclinical Alzheimer’s Disease

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1. Active walking slows preclinical AD cognitive decline;
2. Higher AD vulnerability benefits more from walking;
3. Slower WMH rise partially mediates walking-cognition link

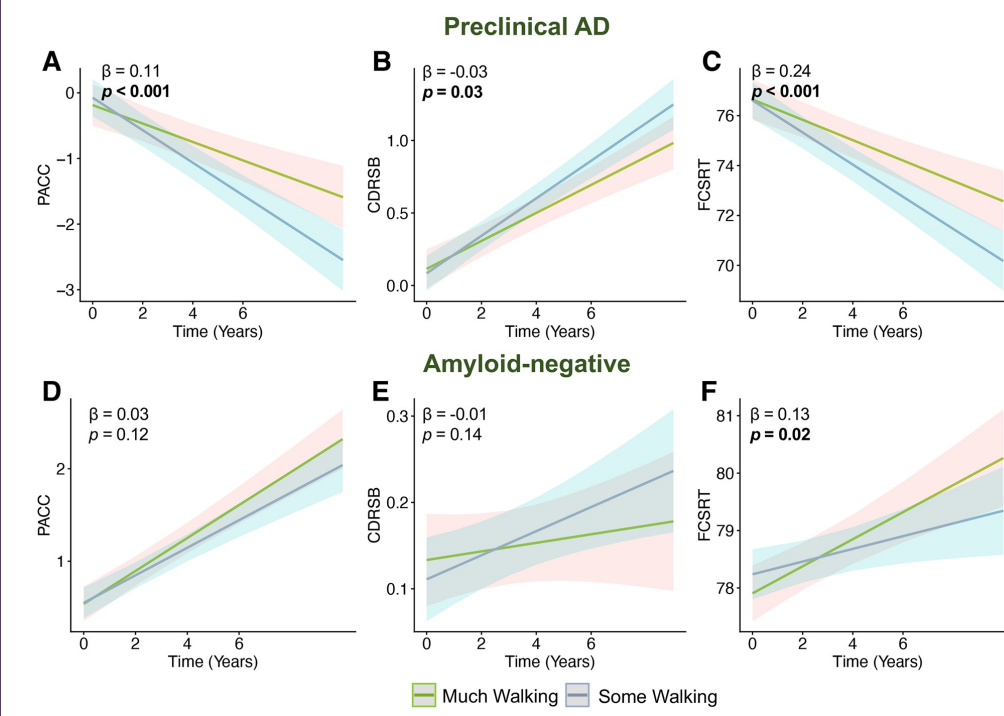
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INTRODUCTION	METHODS
Although physical activity benefits cognition, the efficacy, priority subpopulations, and underlying pathways of habitual walking in preclinical Alzheimer’s disease (AD) remain elusive.	We examined how regular walking duration affects cognitive and functional change in 484 β -amyloid ($A\beta$)-negative and 535 $A\beta$ -positive cognitively unimpaired (CU) older adults. Linear mixed models were utilized to assess the walking-cognition association, effect modification by biological profiles (age, sex, genetic risk, AD pathology), and the mediating role of WMH.

Table 1. Demographic	Preclinical AD (N=535)			$A\beta$ -Negative (N=484)		
	Some Walking	Much Walking	p	Some Walking	Much Walking	p
	N=293	N=242		N=267	N=217	
Age, years, mean (SD)	72.2 (5.08)	71.5 (4.73)	0.105	70.5 (4.38)	70.5 (4.23)	0.859
Education, years, mean (SD)	16.6 (2.74)	16.7 (2.94)	0.715	16.9 (2.53)	16.7 (2.74)	0.574
Sex (n, %)			0.598			0.141
Female	176 (60.1%)	139 (57.4%)		170 (63.7%)	123 (56.7%)	
Male	117 (39.9%)	103 (42.6%)		97 (36.3%)	94 (43.3%)	
APOE Status (n, %)			0.748			0.607
APOE4 Carrier	168 (57.3%)	143 (59.1%)		60 (22.5%)	54 (24.9%)	
APOE4 Non-Carrier	125 (42.7%)	99 (40.9%)		207 (77.5%)	163 (75.1%)	
Baseline PACC Scores	-0.07 (2.65)	0.02 (2.69)	0.697	0.96 (2.06)	0.68 (2.64)	0.212
Baseline Centiloids	66.6 (32.8)	67.3 (32.7)	0.843	4.60 (11.9)	5.30 (12.4)	0.570
Daily Walking Duration (mins)	42.0 (23.3)	72.3 (36.7)	<0.001	39.9 (21.4)	72.9 (38.9)	<0.001

Compared with the Much Walking group, the Some Walking group reported significantly less daily walking duration in both the preclinical AD (mean difference = -30.3 min, $t = -11.14$, 95%CI, -35.66 to -24.96) and the normal aging group (mean difference = -33 min, $t = -11.30$, 95%CI, -38.97 to -27.41).

Figure 1. The association between walking groups and longitudinal cognitive trajectories in preclinical AD and normal aging groups.



In the preclinical AD group, the Much Walking was associated with a slower annual decline in PACC scores (95%CI, 0.05 to 0.16) and FCSRT scores (95%CI, 0.10 to 0.38), as well as a decelerated annual increase in CDR-SB scores (95%CI, -0.06 to -0.004) compared with the Some Walking group (Fig. 1A-C). In the amyloid-negative group, a faster increase in FCSRT scores was observed in the Much Walking group relative to the Some Walking group (95%CI, 0.02 to 0.23) (Fig. 1D-F). The Much Walking group indicated an attenuated decline in Logical Memory (95%CI, 0.02 to 0.15) and DSST (95%CI, 0.13 to 0.36) than the Some Walking group (Fig. 2).

Figure 2. Effects of walking groups on domain-specific cognition change in preclinical AD

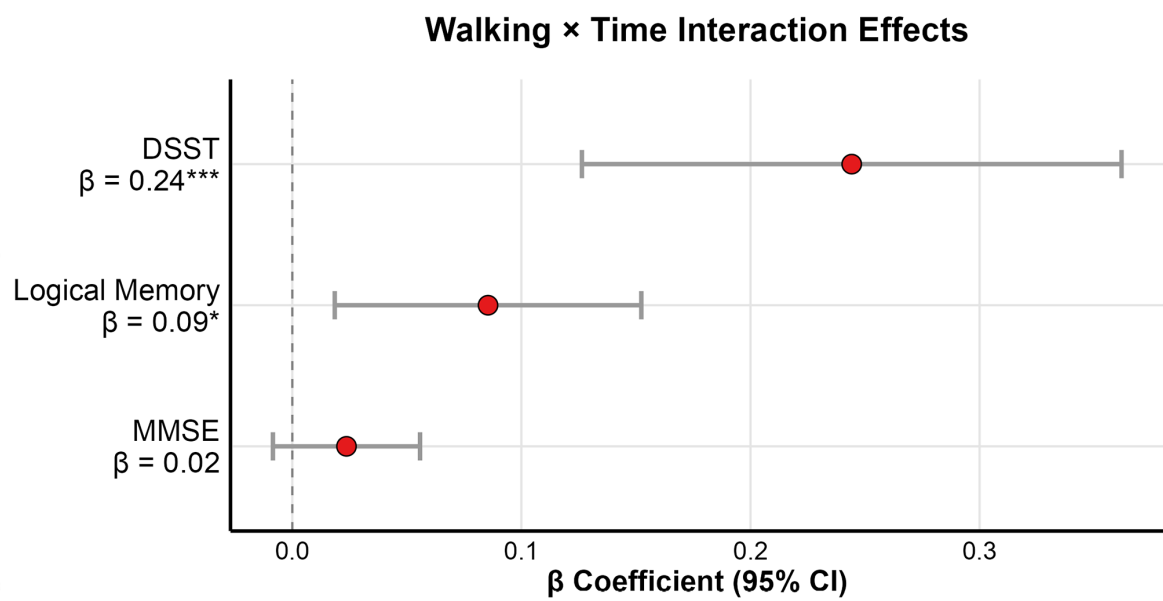
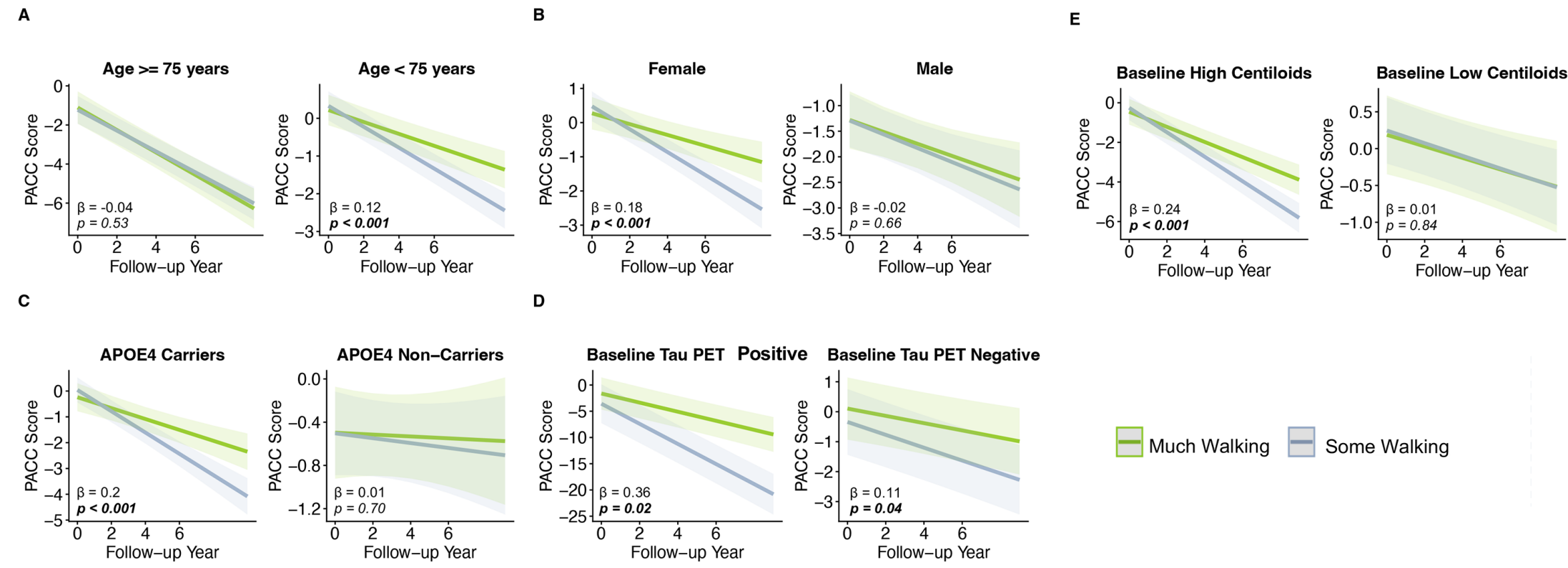
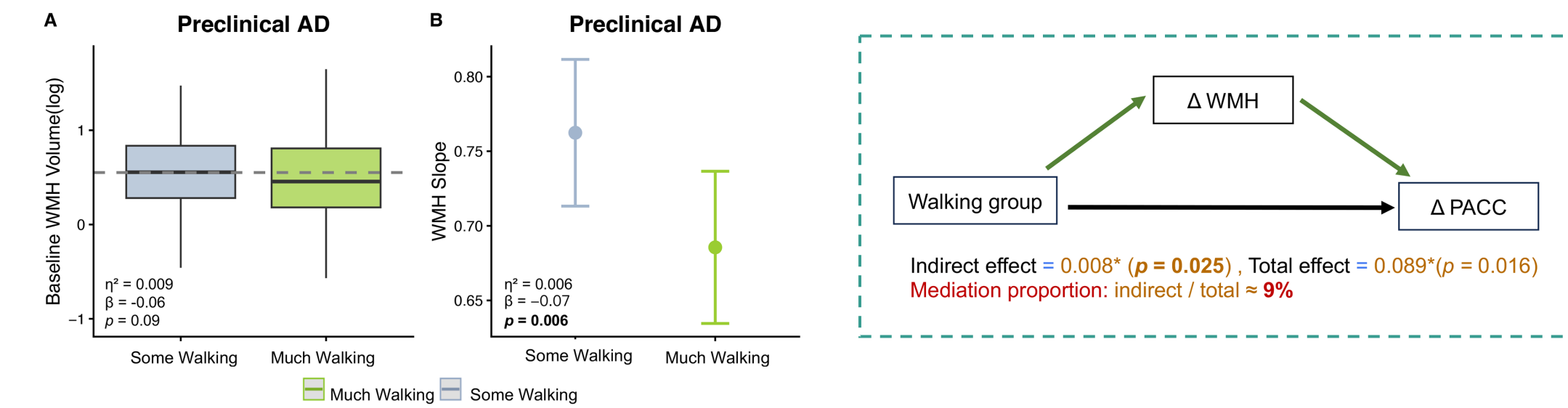


Figure 3. Stratified interaction analyses of walking groups: age, sex, APOE status, and baseline pathological burden in preclinical Alzheimer’s disease.

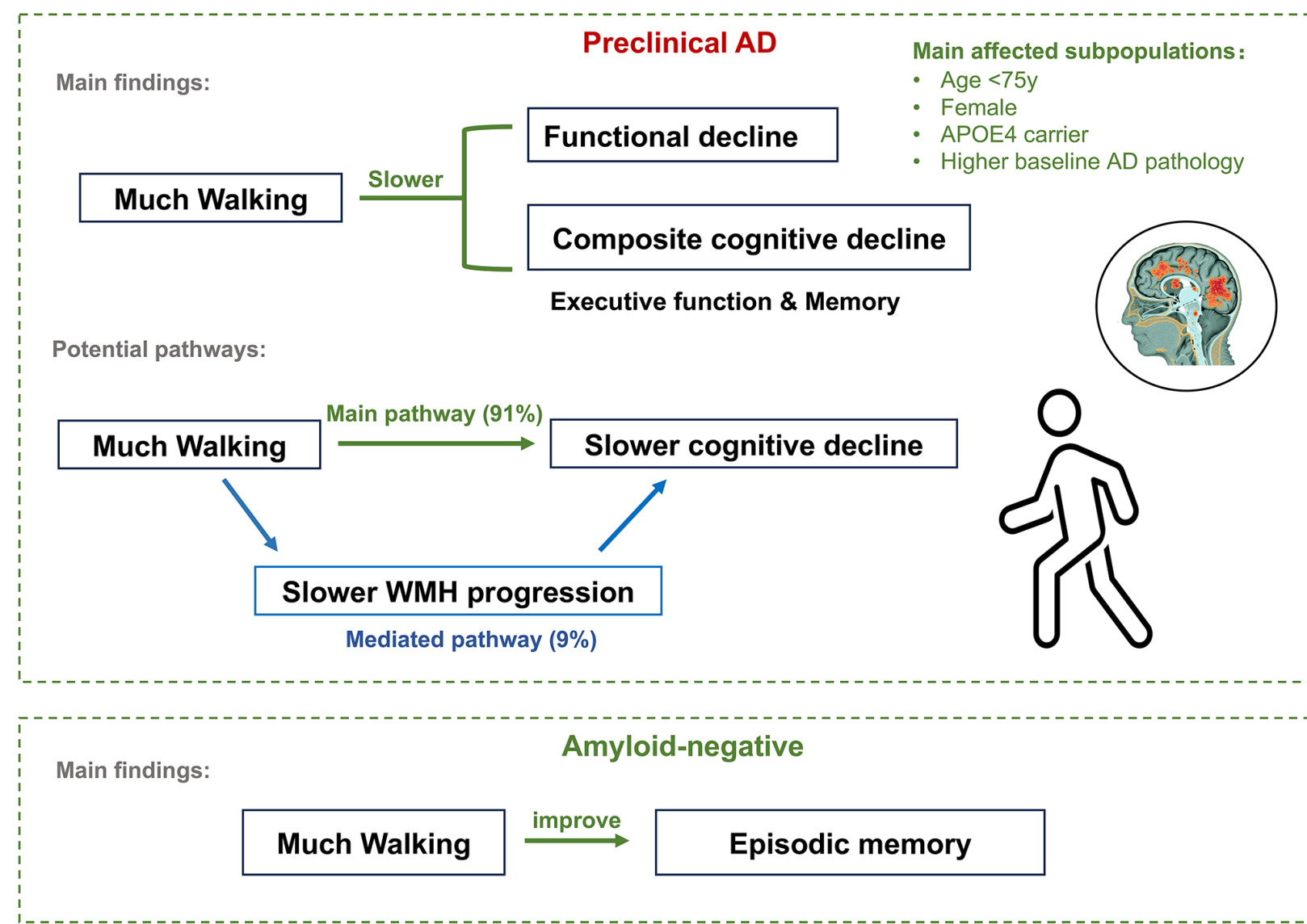


Compared with the Some Walking group, the Much Walking group exhibited significantly slower annual PACC decline among participants aged <75 years, and APOE ϵ 4 carriers (Fig. 3A-C). Moreover, the protective association was amplified in individuals with tau PET and higher Centiloid values (Fig. 3D-E).

Figure 4. Associations between Walking Groups and White Matter Hyperintensities, and the Mediating Role of WMH Change in the Relationship between Walking Groups and Cognitive Decline



The Much Walking group demonstrated a lower baseline WMH volume and a slower rate of WMH volume increase compared with the Some Walking group (Fig.4A-B). Mediation analysis further revealed significant indirect effect of WMH slope on cognitive change ($\beta = 0.01$, $p = 0.02$) was observed. The total effect of the walking group on cognitive change was significant ($\beta = 0.09$, $p = 0.02$). With the inclusion of the mediator, the effect stayed significant (indirect effect: $\beta = 0.08$, $p = 0.03$), accounting for 9% of the total effect. All pathways retained significance after FDR correction. This demonstrates that WMH partially mediates the association between longer walking duration and cognitive benefits in preclinical AD.



The brain amyloid figures were generated by Seedream 4.5(Doubao AI)

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