

Table 1**Potential mechanisms for the effects of exercise on depression**

	Theory	Comments
Biological	Inflammation may disrupt synthesis, reuptake and metabolism of neurotransmitters, affect the HPA axis, and inhibit neurogenesis ¹²	● Depression is associated with increased levels of inflammatory cytokines. Exercise has been shown to have anti-inflammatory effects in subjects who are not depressed ● In the TREAD study^{12,13} of depressed subjects with partial response to SSRIs, higher baseline TNF alpha levels were associated with a greater decrease in depressive symptoms over the period of exercise ($P < 0.0001$). There was a significant correlation between changes in IL-1 levels and depressive symptoms ($P < 0.04$). High TNF alpha may differentially predict better outcomes with exercise, as opposed to antidepressant medications for which high TNF alpha is linked to poor response ● Exercise may be a more effective treatment for depression associated with other comorbid inflammatory conditions, such as the metabolic syndrome, diabetes, arthritis etc
	Neurogenesis	Evidence exists, largely from rat studies, that exercise mediates neurogenesis, possibly by increasing levels of beta endorphins, vascular endothelial growth factor (VEGF), brain-derived neurotrophic factor (BDNF), and serotonin. ¹⁴ More recent evidence in humans suggests that the effect of exercise on depression is <i>not</i> mediated by BDNF ¹⁵
	Serotonin	Lipolysis with exercise may alter the distribution of tryptophan, a precursor for serotonin. ¹⁶ Reduction in plasma serotonin is seen with antidepressants and with exercise ¹⁷
Psychological	HPA axis	Depression is associated with high basal levels of cortisol. Exercise has been shown to reduce levels of cortisol in people with depression ¹⁸
	Cerebral blood flow and glucose metabolism	EEG changes in depressed elderly patients have been correlated with cerebral blood flow and glucose metabolism. Exercise reverses such EEG changes, ¹⁹ possibly by increasing cerebral blood flow
	Self-esteem	Mastery of a new skill ⁵ and positive feedback from others ⁷ may increase feelings of self-esteem and therefore improve mood
	Distraction	Exercise may distract participants from persistent negative thoughts
	Motivation from, and therapeutic relationship with, instructor	Support from a trained instructor using motivational and psychosocial techniques improved adherence to an exercise programme in middle-aged women ⁹
	Behavioural activation	CBT for depression typically includes a 'behavioural activation' component: participants schedule activities, and in completing these activities have a sense of achievement, an improvement in mood, and an increased likelihood of engaging in further activities
Social	Social contact	It is not clear if the effects of exercise are mediated by participation in group activity, or if solitary exercise has similar effects