

## What are the most effective interventions to reduce childhood obesity?

**EVIDENCE-BASED ANSWER** Efforts to increase physical activity or decrease sedentary activities have shown some short-term benefit, and adding dietary changes may be more effective. Aiming interventions at parents, intensive family therapy, comprehensive school-based programs, and selecting motivated children for subspecialty care may improve success. (Grade of recommendation: B, based on poor-quality randomized controlled trials [RCTs] and heterogeneous systematic reviews.) Other potentially effective short-term strategies include screening with body mass index (BMI) for age (grade of recommendation: C, extrapolation from cohort studies and ecological research) or dietary counseling (grade of recommendation: D, conflicting poor-quality RCTs). No drugs are currently approved for pediatric obesity therapy in the United States.

**EVIDENCE SUMMARY** Pediatric obesity increases the risk of adverse outcomes in adulthood, independent of adult BMI.<sup>1</sup> Trials aiming to reduce childhood obesity suffer from serious methodological constraints. No long-term (> 2 years) evidence is available. Many apparently efficacious interventions are beyond the scope of primary care physicians. A detailed summary is available online at <http://www.FPIN.org>.

Several studies have examined the value of isolated changes in either diet or activity level. Randomized controlled trials and retrospective cohort studies of dietary advice alone show short-term efficacy (weeks to months).<sup>1</sup> Most involve intensive subspecialty care for extremely obese children who are 120% to 140% over their ideal body weight. Trials without careful selection of motivated children had dropout rates up to 87%. One Italian RCT showed a 12% reduction in the number of obese children in schools receiving multimedia dietary advice compared with a 5% to 6% increase in those schools receiving only written or no advice.<sup>2</sup> Several RCTs reduced obesity by introducing or improving school-based physical activity.<sup>1</sup> Two RCTs that discouraged sedentary activity through counseling or school-based programs also reduced obesity.<sup>3,4</sup>

Two larger trials integrated diet and exercise advice into school curricula. One study emphasized improving school menus, but no difference was observed because children compensated by overeating at home.<sup>5</sup> The other emphasized reducing sedentary activities and found lower obesity rates in the intervention schools, but only for girls.<sup>6</sup> A third trial pro-

vided family-based dietary and behavior counseling, but emphasized either increasing physical activity or decreasing sedentary activity.<sup>7</sup> Both strategies resulted in reduced obesity compared with controls. A systematic review supported the combined approach of these trials, finding diet and exercise interventions superior to diet interventions alone.<sup>8</sup>

Some evidence supports focusing on the family rather than just the child. A systematic review found that family therapy prevented pediatric obesity.<sup>9</sup> An RCT found that focusing on parents as the sole change agent was superior to targeting the child.<sup>10</sup>

**RECOMMENDATIONS FROM OTHERS** Expert consensus promotes screening because of obesity's increasing incidence and associated morbidity and mortality.<sup>11</sup> The Maternal and Child Health Bureau recommends a primary goal of healthy eating and activity. They recommend treating when the body mass index is >95th percentile, and assessing the child and family's willingness to change. Primary strategies are to begin early, involve the family, promote parenting skills, and increase activity and reduce high-calorie food intake. They also recommend ongoing support to maintain weight loss.<sup>9</sup>

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**What is the target for low-density lipoprotein cholesterol in patients with heart disease?**

**EVIDENCE-BASED ANSWER** Large published randomized controlled trials (RCTs) show that pravastatin and simvastatin are well-tolerated and reduce major coronary events such as death, myocardial infarction, and revascularization by about 25%. The Heart Protection Study suggested this benefit is noted even among individuals with pretreatment low-density lipoprotein (LDL) cholesterol of less than 100 mg/dL. Fluvastatin reduces major coronary events, but current studies are too small to prove reduced overall mortality. The best evidence to date suggests that most patients at significant risk for major coronary events should be given pravastatin or simvastatin 40 mg daily, without concern for the initial or follow-up LDL levels. (Grade of recommendation: A, based on large randomized trials.)

**EVIDENCE SUMMARY** The evidence is solid to support the use of HMG-CoA reductase inhibitors (statins) for patients with coronary artery disease (CAD). The Scandinavian Simvastatin Survival study used simvastatin 20 mg daily unless total cholesterol levels did not decrease to less than 200 mg/dL.<sup>1</sup> The Long-Term Intervention with Pravastatin in Ischaemic Disease study randomized patients to pravastatin 40 mg daily or placebo, without titration.<sup>2</sup> The intervention arm in the Cholesterol and Recurrent Events trial was also pravastatin 40 mg daily, with cholestyramine added if the LDL level remained higher than 175 mg/dL.<sup>3</sup> The Lescol Intervention Prevention study randomized patients after angioplasty to fluvastatin 40 mg twice daily or placebo.<sup>4</sup> The Heart Protection Study used simvastatin 40 mg daily, without titration.<sup>5</sup> No RCTs have evaluated the clinical benefit of adding medications to adequate doses of statins to lower LDL to less than 175 mg/dL. See Table of major RCTs with clinical outcomes.

Subgroup analyses of earlier major RCTs had suggested that patients with CAD and low initial LDL levels (< 125 mg/dL) have little to gain from pravastatin.<sup>2,3</sup> However, the Heart Protection Study enrolled 20,000 people with CAD or equivalent (diabetes, peripheral vascular disease, stroke, etc).<sup>5</sup> The study demonstrated a reduction of major coronary events with simvastatin, with numbers needed to treat (NNT) of 19 ( $P < .0001$ ); the NNT for reduction in all-cause mortality was 55 ( $P = .0003$ ). The benefit of

simvastatin was noted in virtually every predefined subgroup, including individuals older than 70 years, women, and patients without known CAD (but with CAD equivalents).

Notably, no difference in benefit was found between patients with different pretreatment LDL levels. A significant reduction in major vascular

events was noted even for the 3400 subjects with pretreatment LDL levels of less than 100 mg/dL (NNT = 22,  $P = .0006$ ). A greater percentage reduction in LDL with medication did not predict better clinical outcomes.<sup>5</sup>

**RECOMMENDATIONS FROM OTHERS** The National Cholesterol Education Project (NCEP) recommends that patients with CAD and an LDL of more than 130 mg/dL adopt therapeutic lifestyle changes and start LDL-lowering medication, usually a statin. For patients with LDL between 100 and 130 mg/dL, the NCEP recommends therapeutic lifestyle changes, with the option of adding a statin. For patients with LDL less than 100 mg/dL, maintenance of LDL control is recommended with therapeutic lifestyle changes. For patients with high initial LDL levels that stay above 100 mg/dL on statin therapy, the NCEP recommends that additional medications, such as nicotinic acid or fibrates, as well as intensive therapeutic lifestyle changes, be considered.<sup>6</sup>

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**TABLE**

**LDL levels and relative risk of major coronary events after treatment**

Study, year	N	Intervention medication	LDL level, mg/dL		Relative risk of major coronary events
			Control group	Intervention group	
4S, <sup>1</sup> 1994	4444	Simvastatin 20 mg/d*	190	122	0.66 (0.59-0.85)
CARE, <sup>3</sup> 1996	4159	Pravastatin 40 mg/d	139	97	0.76 (0.64-0.91)
LIPID, <sup>2</sup> 1998	9014	Pravastatin 40 mg/d	150	113	0.76 (0.68-0.85)
LIPS, <sup>4</sup> 2002	1677	Fluvastatin 80 mg/d	132	100	0.78 (0.64-0.95)
HPS, <sup>5</sup> 2002	20,536	Simvastatin 40 mg/d	127	89	0.76 (0.72-0.81)

\*Increased to 40 mg/d if total cholesterol did not drop to less than 200 mg/dL.

4S, Scandinavian Simvastatin Survival Study; CARE, Cholesterol and Recurrent Events trial; HPS, Heart Protection Study; LDL, low-density lipoprotein; LIPID, Long-Term Intervention with Pravastatin in Ischaemic Disease study; LIPS, Lescol Intervention Prevention Study.

**What medications are effective for treating symptoms of premenstrual syndrome (PMS)?**

EVIDENCE-BASED ANSWER Vitamin B6 (50–100 mg/d) and elemental calcium (1200 mg/d) are safe, inexpensive, and moderately effective (Table) (grade

Agents for treating symptoms of premenstrual syndrome			
Medication	Sample drug and dose	Adverse effects	Benefit
Vitamin B6 <sup>1</sup>	50–100 mg/d	Peripheral neuropathy	OR = 2.32 (95% CI 1.95–2.54)
Elemental calcium <sup>2</sup>	1200 mg/d	Same as placebo	NNT = 6 for 50% symptom reduction
SSRIs <sup>3</sup>	Fluoxetine 20 mg/d	Insomnia, headache, nausea, dizziness	NNT = 4–11
Benzodiazepines <sup>4</sup>	Alprazolam 0.25–0.5 mg tid/qid in luteal phase	Habituation	NNT = 3 for 50% symptom reduction
GnRH agonists <sup>5</sup>	Danazol 200–400 mg/d	Hypoestrogenic Androgenic	Benefit unclear Benefit unclear

GnRH, gonadotropin-releasing hormone; NNT, number needed to treat; SSRIs, selective serotonin reuptake inhibitors.

of recommendation: B). Selective serotonin reuptake inhibitors (SSRIs) and some other antidepressants are more effective, but are also more costly and more likely to cause side effects or treatment dropout (grade of recommendation: A). Antidepressant dosing only during the luteal phase may be effective and more tolerable (grade of recommendation: B). Alprazolam (generally 0.25–0.5 mg 3 times a day during luteal phase) may be effective for treating mood or anxiety symptoms (grade of recommendation: B). Hormonal therapies (oral contraceptives, gonadotropin-releasing hormone agonists, danazol, estrogen) lack convincing evidence of efficacy and cause many side effects; progesterone is no more beneficial than placebo (grade of recommendation: B). There is no convincing evidence of benefit from diuretics, magnesium, beta-blockers, or lithium (grade of recommendation: C).

EVIDENCE SUMMARY Pooled results of 9, generally poor-quality studies of Vitamin B6 show some benefit.<sup>1</sup> Doses higher than 100 mg/d may cause peripheral neuropathy. Three small studies in the 1980s suggested possible benefit of Vitamin E; however, these studies have not been further replicated. One well-designed, randomized controlled trial of calcium therapy showed > 50% decrease in symptom complex scores after 3 months in more than half of subjects taking 1200 mg/d supplemental elemental calcium (NNT=6).<sup>2</sup>

Among SSRIs, fluoxetine (20 mg/d) is well-studied and effective.<sup>3</sup> Other SSRIs, including sertraline, paroxetine, fluvoxamine, and venlafaxine, and

clomipramine (a tricyclic with serotonin reuptake inhibitor activity), also show benefit but are less well studied. Luteal phase-only dosing may be equally or more effective than continuous dosing for some SSRIs. Benzodiazepines have shown mixed results in treating PMS, and overall their benefit appears smaller than that of SSRIs.<sup>4</sup> Luteal phase-only dosing theoretically reduces the risk of benzodiazepine withdrawal or dependence, but published data are rare.

Gonadotropin-releasing hormone agonists may be effective, but troublesome anti-estrogenic side effects limit their utility. Estrogen and progesterone “add-back” therapy to counter side effects further complicates this approach. The gonadotropin inhibitor danazol has a high treatment dropout rate at higher doses (200–400 mg/d continuously), but can be effective in individuals who are able to tolerate it<sup>5</sup>; however, danazol is expensive and causes significant androgenic side effects. Lower-dose danazol (200 mg/d luteal phase only) is better tolerated but ineffective.<sup>6</sup> A meta-analysis of progesterone found no evidence to support its efficacy.<sup>7</sup> Oral contraceptives are ineffective for global symptoms, and may actually cause PMS symptoms in some women.

RECOMMENDATIONS FROM OTHERS The American College of Obstetricians and Gynecologists recommend that patients with mild to moderate PMS should receive supportive, lifestyle, and dietary interventions. For severe PMS, SSRIs are the initial drug of choice. Alprazolam may be useful when these interventions are ineffective. Consider oral contraceptives for primarily physical symptoms and reserve gonadotropin-releasing hormone for severe cases unresponsive to other treatments.<sup>8</sup>

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