

risk of ASCVD. High-intensity statins are first line, but many patients with FCHL require combination therapy that includes ezetimibe, a PCSK9 inhibitor, and/or bempedoic acid.

## ■ SECONDARY CONTRIBUTORS TO ELEVATED LEVELS OF APOB-CONTAINING LIPOPROTEINS

There are many “secondary” factors that contribute to dyslipidemia ([Table 407-3](#)), often acting in concert with polygenic predisposition as reviewed above. Some primarily affect TGs, some primarily affect LDL-C, and some influence both, with a great deal of variability. Here the major secondary contributors are reviewed.

**Secondary Factors That Primarily Elevate TG Levels • HIGH-CARBOHYDRATE DIET** Dietary carbohydrates are utilized as a substrate for fatty acid synthesis in the liver. Some of the newly synthesized fatty acids are esterified, forming TGs, and secreted in VLDL. Thus, excessive intake of calories as carbohydrates, which is frequent in Western societies, leads to increased hepatic VLDL-TG secretion and elevated TG levels. Reduction in carbohydrate consumption can have a substantial effect in reducing TG levels, although replacing carbohydrates with saturated fat can elevate LDL-C levels.

**OBESITY, INSULIN RESISTANCE, AND TYPE 2 DIABETES** ([See also Chaps. 401–403](#)) Obesity, insulin resistance, and type 2 diabetes mellitus are the most frequent contributors to dyslipidemia, primarily by influencing TGs. The increase in adipocyte mass and accompanying decreased insulin sensitivity associated with obesity have multiple effects on lipid metabolism, with one of the major effects being excessive hepatic VLDL production. More free fatty acids are delivered from the expanded and insulin-resistant adipose tissue to the liver, where they are reesterified in hepatocytes to form TGs, which are packaged into VLDLs for secretion into the circulation. In addition, the increased insulin levels promote increased fatty acid synthesis in the liver. In insulin-resistant patients who progress to type 2 diabetes mellitus, dyslipidemia remains common, even when the patient is under relatively good glycemic