**FIGURE 29.1** Lack of correlation between high-molecular-mass Aβ aggregates and toxicity. (A). *daf-2* RNAi protects Aβ worms from the paralysis phenotype associated with Aβ expression. (B). The *daf-2* RNAi-mediated protective effect is *daf-16* and *hsf-1* dependent. *daf-2* RNAi protected worms from paralysis when diluted with EV bacteria but not when mixed with either *daf-16* or *hsf-1* RNAi bacteria. (C) Aβ worms were grown on RNAi bacteria as indicated. At day 3 of adulthood the worms were homogenized, spun, and debris was separated from the soluble fraction. Aβ contents in worm debris were analyzed using Western blot and 6E10 antibody. (From [10], with permission of AAAS.) (D) In vitro kinetic aggregation assay. The typical lag phase that is associated with in vitro aggregation of Aβ can be shortened by seeding of the reaction with previously aggregated Aβ. This technique has been exploited to measure Aβ aggregate content in worm samples. (E) Aβ seed contents of worms grown on RNAi bacteria (as indicated) were evaluated using kinetic aggregation assay. (From [10], with permission of AAAS.) (F) Quantification of three independent in vitro kinetic aggregation assays [as in (E)].
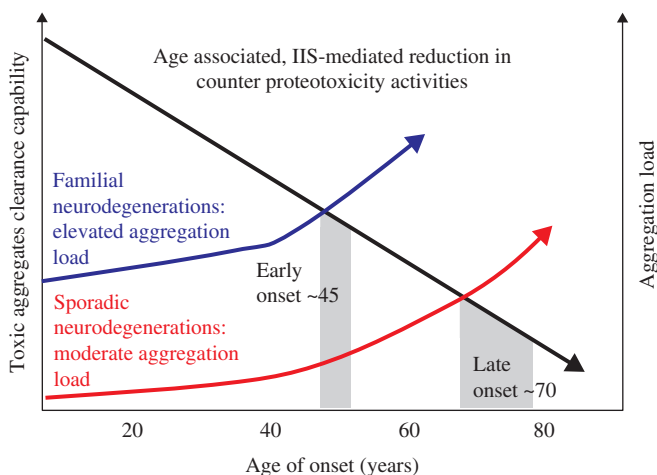
FIGURE 29.3 The balance between the production of toxic protein aggregates and the aging-associated reduction in counter-proteotoxicity activities determines the age at which the amount of toxic aggregates required for disease onset will cross the threshold level. A higher aggregation load and lower protective activities will lead to early onset, while a lower aggregation load and higher protective capabilities will postpone the disease age of onset. This model proposes that the similar ages of onset of distinct neurodegenerations stem from one phenomenon: the age-related decline in the natural counter-proteotoxicity activities. (From *Nature Reviews Neuroscience*, 9, 759–767.)