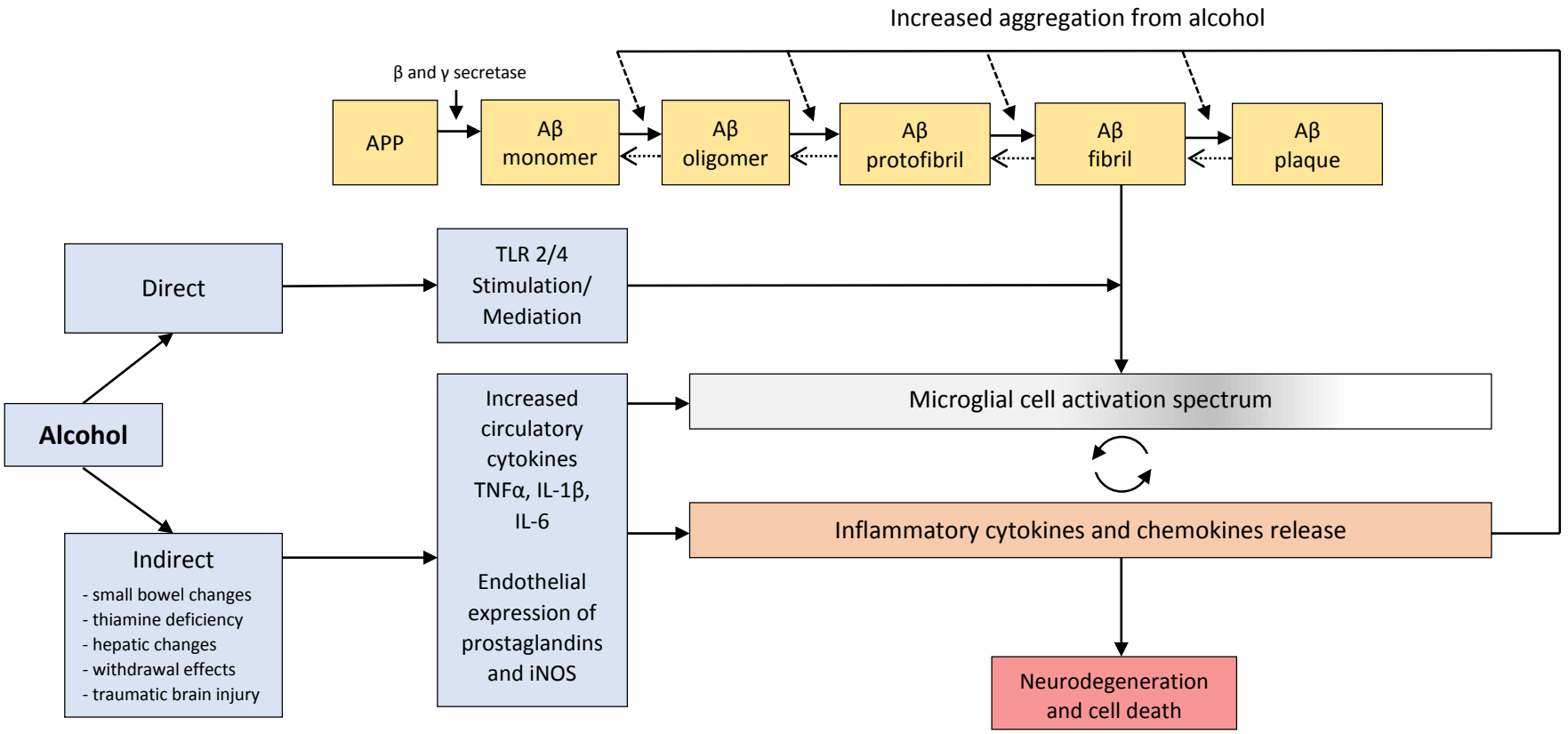
Increased aggregation from alcohol
β and γ secretase
APP
Aβ monomer
Aβ oligomer
Aβ protofibril
Aβ fibril
Aβ plaque
Direct
TLR 2/4 Stimulation/ Mediation
Alcohol
Increased circulatory cytokines TNFα, IL-1β, IL-6
Endothelial expression of prostaglandins and iNOS
Microglial cell activation spectrum
Inflammatory cytokines and chemokines release
Indirect
- small bowel changes
- thiamine deficiency
- hepatic changes
- withdrawal effects
- traumatic brain injury
Neurodegeneration and cell death

Figure 1 – Proposed links between alcohol and Aβ cascade in AD through inflammatory processes. Aβ peptide is cleaved from the transmembrane amyloid precursor protein (APP) by β and γ secretases. There is an increase in production or reduced clearance of Aβ with the likelihood of conversion shown by solid arrows, and less conversion illustrated by dotted arrows. Different forms of Aβ affect microglial cell activation differently, and Aβ fibrils are shown to activate microglial cells, leading to inflammatory cytokines and chemokines release, further both re-activating microglial cells, and also causing increased aggregation of Aβ towards plaque forms. This self-perpetuating cycle leads to neurodegeneration and cell death. It is suggested that alcohol acts both directly and indirectly on this system. Directly alcohol causes TLR2/4 stimulation and together with fAβ it leads to increased microglial activation, and greater inflammatory cytokines and chemokine release. Indirectly alcohol via small bowel, hepatic and withdrawal effects causes increased circulatory cytokines, in particular TNFα, IL-1β, IL-6 and endothelial expression of prostaglandins and iNOS which cause direct microglial cell activation, and contribute to neuroinflammation by cytokines and chemokines release. The summation of effects results in more neurodegeneration and cell death, greater microglial burnout, and increased aggregation of Aβ due to a combination of increased inflammatory mediators, and decreased or saturated microglial cells.