It is pressing to investigate the influence factors of eutrophication in Dongting Lake, which is the second largest freshwater lake in China and is faced with more and more serious eutrophication problems by natural and man-made factors in recent years. In this study, a new multivariate analysis approach integrating the maximum likelihood estimation structural equation modelling (ML-SEM) with neural network method is proposed. Twenty-seven variables indicating water quality from 2005 to 2012 were derived from the Dongting Lake Ecological Environment Monitoring Center of Hunan Province. The results showed that: (1) temperature (T) and hydraulic gradient (HG) had the most positive influence on chlorophyll-a (Chl-a) with a sensitivity ratio of 1.218 and 1.039, respectively, (2) transparency (SD) had the most negative effect on Chl-a concentration and (3) Chl-a increased quickly and reached the highest level when total phosphorus (TP) levels were from 0.08 mg/L to 0.12 mg/L. These results would provide guidance for eutrophication control strategies for Dongting Lake. By combining ML-SEM with artificial intelligence technique such as neural network, this study examined the causal and nonlinear relationships involved in the eutrophication process.