

No.	Ref.	Methods: Study design Population Inclusion criteria – Definition of Cases, of Exposure Reference Group (Controls) No. of patients (ALS cases, controls; or Exposed, Unexposed) Period of Observation Outcome; Primary outcome variable Masking	Results: Numbers affected among Exposed / Unexposed; Dose – Response results (if available); 95% Confidence Intervals (CI); Significance or Power calculations	Class of Evidence	Comments
A1	[13]	<p>Exploratory case-control study</p> <p><u>Provisional index cases</u>: 1400 mortality cases certified as MND in Japan 1965-1966, verified by consultation with certifying physicians and pathologists.</p> <p><u>Controls</u>: Spouses of patients – matched to gender of patients.</p> <p><u>Cases</u>: 458 men and 254 women with MND (TL=712)</p> <p><u>Controls</u>: 216 widowers; 421 widows of patients</p> <p><u>Exposure</u>: Smoking determined by questionnaire – further detail not available. Widower(s) surrogate respondents for deceased patients.</p> <p>One of approximately 10 questions (broadly defined) asked.</p> <p><u>Period of observation</u>: Beginning of marriage to clinical onset of MND (first difficulty ultimately shown to be due to MND)</p> <p><u>Masking</u>: None.</p> <p><u>Primary outcome variable</u>: % smokers in cases and controls</p>	<p>Smoking in men: Cases 74.3% Controls 77.1% RR 0.95 Smoking in women: Cases 14.1% Controls 15.8% RR 0.92</p> <p>95% confidence interval: not provided. P-value: inferred not significant. Power calculations: not provided. No dose data.</p>	IV	<p>Overmatching of controls. Smoking by male spouses of female patients may be the risk factor for ALS in those female patients, via passive smoking, and thus be as frequent as smoking by male patients: biases RR to 1.0.</p> <p>Unstated if smoking is “ever smoked” or “smoked at time of disease onset.” Disease would cause some smokers to quit.</p> <p>Lack of quantitative data biases RR to 1.0</p>
A2	[13]	<p>Case-control study by research group organized in 1973</p> <p><u>Index cases</u>: 158 surviving hospital ALS patients (104 men, 54 women) in arbitrary areas of Japan</p> <p><u>Controls</u>: Unrelated non-neurologic patients or normal, matched on gender, age +/- 5 years, and residence</p> <p><u>Exposure</u>: Determined by questionnaire administered to patients and control by neurologist who diagnosed the</p>	<p><u>Smoking in men</u>: Cases 33.3%, Controls 30.3%; RR 1.05 <u>Smoking in women</u>: Cases 1.9%, Controls 0.</p> <p>95% confidence interval: not provided. P-value: inferred &gt;0.05 Power calculations: not provided. No dose data.</p>	IV	<p>Unaccounted difference in % of smokers among controls, compared to study A1, suggests that the patients and control samples may not be representative of the general population.</p>

		<p>patient.  <u>Period of observation:</u> Birth till clinical disease onset in cases and same &lt;date&gt; in matched control.  <u>Masking:</u> None                  22 questions (broadly defined) asked.  <u>Primary outcome variable:</u> % smokers in cases and controls</p>		<p>Failure to use optimal statistical technique (discordant pair analysis, see Doll and Hill).                  Unstated if smoking is “ever smoked” or “smoked at time of disease onset.” Disease would cause some smokers to quit.                  Lack of quantitative data biases                  RR to 1.0</p>
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Table e-2. Evidence table for a representative pre-1990 article, provided to make explicit the rationale for classifying the evidence of this early article as Class IV.

Legend: RR= relative risk. WFN = World Federation of Neurology. (WFN criteria = El Escorial criteria). OR = odds ratio. IR = incidence rate. CI = confidence interval. MND = motor neuron disease, comprises ALS (amyotrophic lateral sclerosis), PBP (progressive bulbar palsy) and SPMA (spinal progressive muscular atrophies).