

1 **Table S1.** Detail of the Twenty-Nine Studies Excluded from the Systematic Review

First author, year	Reason of exclusion from the systematic review	Reference
Adornato BT. 1978	Review paper	[1]
Burman JF, Amess JA, et al. 1978	Review paper	[2]
Nunn JF, Chanarin I. 1978	Review paper	[3]
Chanarin I. 1979	Review paper	[4]
Chanarin I. 1980	Review paper	[5]
Nevins MA. 1980	No biological data available	[6]
Gillman MA. 1982	Review paper	[7]
Lunsford JM, Wynn MH. 1983	Congress abstract	[8]
Koblin DD, Biebuyck JF. 1986	Narrative review	[9]
Ueland PM. 1987	Not in English	[10]
Ruprecht J, Erdmann W, et al. 1989	Not in English	[11]
Ostreicher DS. 1994	Review paper	[12]
Hoerauf K, Koller C, et al. 1995	Not in English	[13]
King M, Coulter C, et al. 1995	No available data	[14]
Jongen JC, Koehler PJ, et al. 1995	Not in English	[15]
Nestor PJ, Stark RJ. 1996	No biological data available	[16]
Takacs J. 1996	Not in English	[17]
Lai NY, Silbert PL. 1997	Congress abstract	[18]
Mayall M. 1999	Review paper	[19]
Alarcia R, Ara JR, et al. 1999	Not in English	[20]
Gothe CJ, Petersson G. 1999	Not in English	[21]
Lindstedt G. 1999	Not in English	[22]
Barbosa L, Leal I, et al. 2000	Not in English	[23]
Vinciguerra C, Chazerain P, et al. 2000	Not in English	[24]
Smith I. 2001	Review paper	[25]
Deleu D, Hanssens Y, et al. 2001	Review paper	[26]
England JM, Linnell JC. 2001	Review paper	[27]
Van Geffen GJ, de Boer HD, et al. 2001	Not in English	[28]
Burman JF. 2003	Editorial	[29]
Erbe RW, Salis RJ. 2003	Narrative review	[30]
Yamada T, Hamada H. 2005	Subject not exposed to N <sub>2</sub> O	[31]
Gerges FJ, Dalal AR. 2006	Previously treated with vitamin B12	[32]
Cohen Aubart F, Sedel F et al. 2007	Not in English	[33]
El Otmani H, El Moutawakil B, et al. 2007	Not in English	[34]
Luzardo GE, Karlinski RA, et al. 2008	Review paper	[35]
El Otmani H, El Moutawakil B, et al. 2009	Not in English	[36]
Paul I, Reichard RR. 2009	Subject not exposed to N <sub>2</sub> O	[37]

<b>Asghar A, Ali FM. 2012</b>	Previously treated with vitamin B12	[38]
<b>Chaugny C, Simon J, et al. 2014</b>	Not in English	[39]
<b>Chin J, Forzani B, et al. 2015</b>	Review paper	[40]
<b>Liakoni E, Liechti ME. 2015</b>	Not in English	[41]
<b>Goodman BP. 2015</b>	Review paper	[42]
<b>van Amsterdam J, Nabben T, et al. 2015</b>	Review paper	[43]
<b>Garakani A, Jaffe RJ, et al. 2016</b>	Review paper	[44]
<b>Ingelmo P, Wei A, et al. 2017</b>	Previously treated with vitamin B12	[45]
<b>Fluegge K. 2017</b>	Review paper	[46]
<b>Stockton L, Simonsen C, et al. 2017</b>	Review paper	[47]

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3 **Table S2.** Detail of the Studies Retained in the Systematic Review

<b>First author, year</b>	<b>Reference</b>
Layzer, 1978	[48]
Layzer, 1978	[49]
Sahenk, 1978	[50]
Gutmann	[51]
Paulson, 1979	[52]
Nunn, 1982	[53]
Blanco, 1983	[54]
Murdoch, 1985	[55]
Heyer, 1986	[56]
Schilling, 1986	[57]
Berger, 1988	[58]
Stabler, 1991	[59]
Vishnubhakat, 1991	[60]
Stacy, 1992	[61]
Hadzic, 1995	[62]
Kinsella, 1995	[63]
McMorrow, 1995	[64]
Rosener, 1996	[65]
Brett, 1997	[66]
Beltramello, 1998	[67]
Pema, 1998	[68]
Jameson, 1999	[69]
Lee, 1999	[70]
Ogundipe, 1999	[71]
Butzkueven, 2000	[72]
Sesso, 1999	[73]
Felmet, 2000	[74]
Marie, 2000	[75]
McNeely, 2000	[76]
Iwata, 2001	[77]
Ilniczky, 2002	[78]
Ng, 2002	[79]
Selzer, 2003	[80]
Waclawik, 2003	[81]
Diamond, 2004	[82]
Doran, 2004	[83]
Miller, 2004	[84]
Ahn, 2005	[85]

Waters, 2005	[86]
Sethi, 2006	[87]
Cartner, 2007	[88]
Levine, 2007	[89]
Shulman, 2007	[90]
Wu, 2007	[91]
Meyers, 2008	[92]
Singer, 2008	[93]
Huang, 2009	[94]
Renard, 2009	[95]
Wijesekera, 2009	[96]
Richardson, 2010	[97]
Tatum, 2010	[98]
Alt, 2011	[99]
Hathout, 2011	[100]
Lin, 2011	[101]
Probasco, 2011	[102]
Ghobrial, 2012	[103]
Hsu, 2012	[104]
Sotirchos, 2012	[105]
Cheng, 2013	[106]
Chiang, 2013	[107]
Gursoy, 2013	[108]
Safari, 2013	[109]
Arshi, 2014	[110]
Dababneh, 2014	[111]
Garakani, 2014	[112]
Hu, 2014	[113]
Rheinboldt, 2014	[114]
Shwe, 2014	[115]
Duque, 2015	[116]
Morris, 2015	[117]
Pugliese, 2015	[118]
Thompson, 2015	[119]
Wolpert, 2015	[120]
Chen, 2016	[121]
Hirvioja, 2016	[122]
Massey, 2016	[123]
Sleeman, 2016	[124]
Buizert, 2017	[125]
Kaski, 2017	[126]
Yuan, 2017	[127]

<b>Chen, 2018</b>	[128]
<b>Egan, 2018</b>	[129]
<b>Johnson, 2018</b>	[130]
<b>Keddie, 2018</b>	[131]
<b>Middleton, 2018</b>	[132]

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6 **Table S3.** Variables Associated with Regular Nitrous Oxide Exposure in Univariate Analyses

	Short exposure to N <sub>2</sub> O			Regular exposure to N <sub>2</sub> O			<i>p</i> -value*
	N	Median	25–75 P	N	Median	25–75 P	
<b>Age (years)</b>	24	47	25–58	76	26	22–33	0.002
<b>Laboratory findings</b>							
Vitamin B12 (pmol/L)	21	74	33–104	61	110	81–194	0.0008
Folate (serum) (µg/L)	9	13.2	7.0–16.1	11	12.7	7.3–14.0	0.68
Hematocrit (%)	5	34.0	26.8–38.5	16	39.3	34.6–44.2	0.23
Hemoglobin (g/dL)	11	11.2	9.5–12.3	32	12.2	8.9–13.8	0.44
Homocysteine (µmol/L)	5	111.0	76.4–142.8	26	46.7	28.2–106.0	0.06
Mean corpuscular volume (fL)	15	104	101–110	40	97	92–101	0.0002
Methylmalonic acid (µmol/L)	0	—	—	16	5.0	1.1–6.6	—
<b>Clinical findings</b>							
	N	Percentage	95% CI	N	Percentage	95% CI	<i>p</i> -value†
Abdominal pain	24	0.0	—	76	4.0	0–8.4	0.99
Agitation	24	4.2	0–12.8	76	1.3	0–3.9	0.42
Anorexia	24	4.2	0–12.8	76	0.0	—	0.24
Apnea	24	4.2	0–12.8	76	0.0	—	0.24
Ataxia	24	8.3	0–20.3	76	13.2	5.4–20.9	0.73
Athetoid movement	24	4.2	0–12.8	76	0.0	—	0.24
Behavior alteration	24	0.0	—	76	7.9	1.7–14.1	0.33
Bulbar paralysis	24	0.0	—	76	1.3	0–3.9	0.99
Chest pain	24	0.0	—	76	1.3	0–3.9	0.99
Mental confusion	24	4.2	0–12.8	76	2.6	0–6.3	0.56
Constipation	24	0.0	—	76	4.0	0–8.4	0.99

<b>Decreased libido</b>	24	0.0	—	76	2.6	0–6.3	0.99
<b>Depression</b>	24	4.2	0–12.8	76	4.0	0–8.4	0.99
<b>Disorientation</b>	24	4.2	0–12.8	76	0.0	—	0.24
<b>Iterative fallings or equilibrium disorders</b>	24	12.5	0–26.8	76	27.6	17.3–37.9	0.17
<b>Fecal incontinence</b>	24	4.2	0–12.8	76	1.3	0–3.9	0.42
<b>Foot pain</b>	24	0.0	—	76	4.0	0–8.4	0.99
<b>Cognitive decline</b>	24	12.5	0–26.8	76	7.9	1.7–14.1	0.44
<b>Headache</b>	24	4.2	0–12.8	76	4.0	0–8.4	0.99
<b>Hyperpigmentation</b>	24	0.0	—	76	4.0	0–8.4	0.99
<b>Hypotonia</b>	24	4.2	0–12.8	76	0.0	—	0.24
<b>Impaired memory</b>	24	4.2	0–12.8	76	5.3	0.1–10.4	0.99
<b>Lethargy</b>	24	8.3	0–20.3	76	0.0	—	0.06
<b>Lhermitte’s sign</b>	24	8.3	0–20.3	76	17.1	8.4–25.8	0.51
<b>Neck pain</b>	24	0.0	—	76	1.3	0–3.9	0.99
<b>Painful erection</b>	24	0.0	—	76	1.3	0–3.9	0.99
<b>Paranoid behavior</b>	24	0.0	—	76	4.0	0–8.4	0.99
<b>Paraplegia</b>	24	4.2	0–12.8	76	0.0	—	0.24
<b>Paresthesia in extremities, numbness, tingling</b>	24	70.8	51.2–90.4	76	82.9	74.2–91.6	0.24
<b>Polyneuropathy</b>	24	0.0	—	76	1.3	0–3.9	0.99
<b>Quadriparesis or paralysis</b>	24	8.3	0–20.3	76	6.6	0.9–12.3	0.67
<b>Respiratory paralysis</b>	24	0.0	—	76	1.3	0–3.9	0.99
<b>Seizures</b>	24	8.3	0–20.3	76	0.0	—	0.06
<b>Spasm</b>	24	0.0	—	76	1.3	0–3.9	0.99
<b>Suicidal thought</b>	24	0.0	—	76	1.3	0–3.9	0.99
<b>Syncope</b>	24	0.0	—	76	1.3	0–3.9	0.99

<b>Tachypnea</b>	24	4.2	0–12.8	76	0.0	—	0.24
<b>Unsteady gait, walking difficulty</b>	24	54.2	32.7–75.7	76	59.2	47.9–70.5	0.81
<b>Urinary incontinence</b>	24	12.5	0–26.8	76	6.6	0.9–12.3	0.39
<b>Urine retention</b>	24	4.2	0–12.8	76	5.3	0.1–10.4	0.99
<b>Vertigo</b>	24	0.0	—	76	1.3	0–3.9	0.99
<b>Visual hallucination</b>	24	4.2	0–12.8	76	1.3	0–3.9	0.42
<b>Vomiting</b>	24	0.0	—	76	1.3	0–3.9	0.99
<b>Weakness</b>	24	25.0	6.3–43.7	76	48.7	37.2–60.2	0.06
<b>Reported diagnoses</b>							
<b>Axonal polyneuropathy</b>	24	12.5	0–26.8	76	10.5	3.5–17.6	0.72
<b>Vitamin B12 deficiency</b>	24	25.0	6.3–43.7	76	10.5	3.5–17.6	0.09
<b>Encephalopathy</b>	24	4.2	0–12.8	76	1.3	0–3.9	0.42
<b>Generalized demyelinating polyneuropathy</b>	24	20.8	3.3–38.4	76	23.7	13.9–33.5	0.99
<b>MTHFR deficiency</b>	24	4.2	0–12.8	76	0.0	—	0.24
<b>Myelopathy</b>	24	16.7	0.6–32.7	76	28.9	18.5–39.4	0.29
<b>Recurrent paraparesis</b>	24	0.0	—	76	1.3	0–3.9	0.99
<b>Subacute combined degeneration</b>	24	37.5	16.6–58.4	76	25.0	15–35	0.29
<b>Toxicity due to N<sub>2</sub>O with no specific diagnosis applied</b>	24	8.3	0–20.3	76	22.4	12.8–32	0.15
<b>Male gender</b>	24	58.3	37.1–79.6	76	60.5	49.3–71.8	0.99
<b>Presence of T2 signal hyperintensity in the spinal cord</b>	16	81.3	59.8–100	59	64.4	51.8–77	0.24

7 IQR: interquartile range; N: total number of studied patients.

8 \* Mann-Whitney *U* test

9 † Fisher’s exact test

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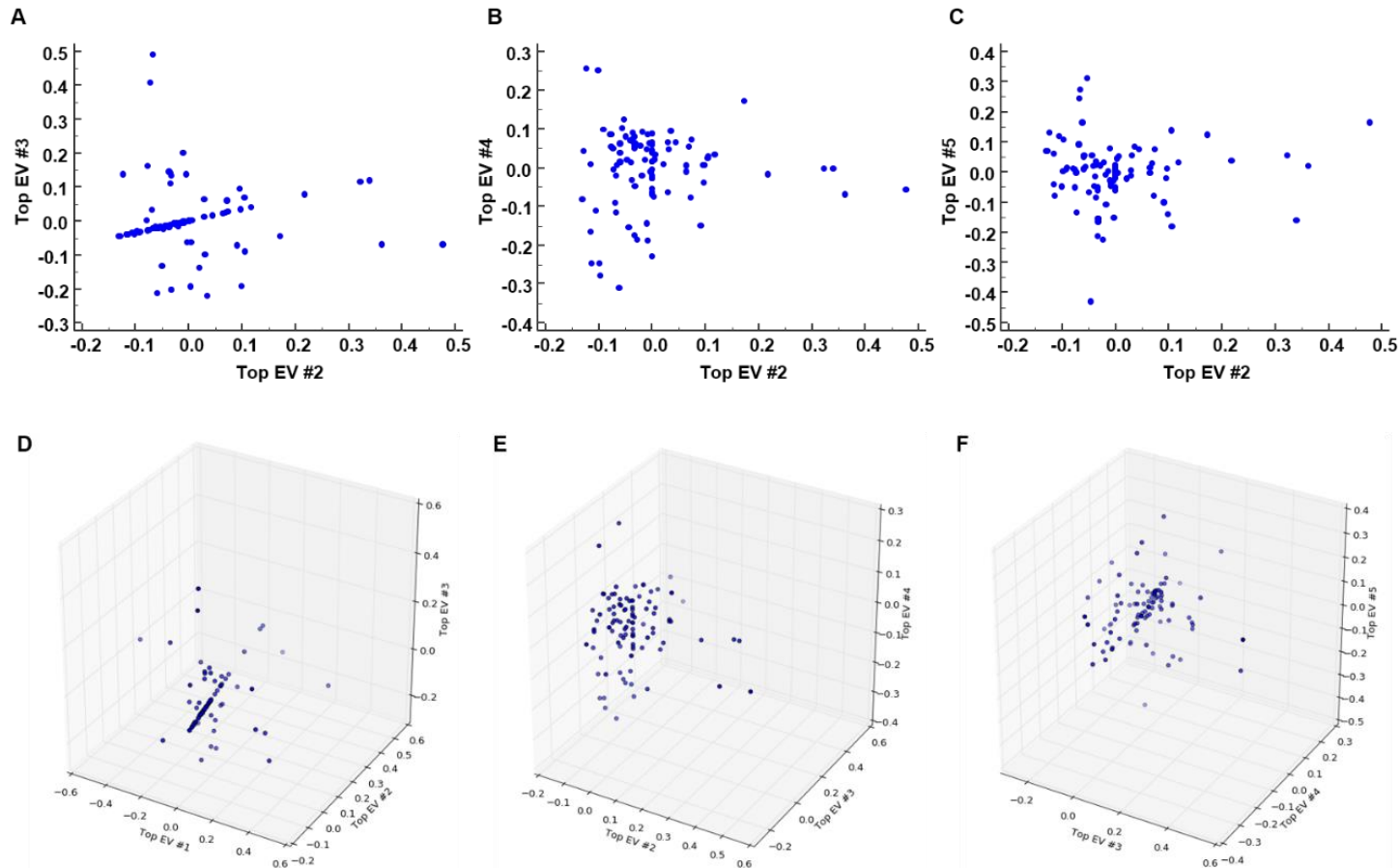
13 **Table S4.** Association Between the Amount of Nitrous Oxide (N<sub>2</sub>O) Exposure and Main Clinical,  
14 Laboratory, and Magnetic Resonance Findings of the N<sub>2</sub>O-Related Disease

<b>Main clinical findings</b>	<b><i>p</i>-value*</b>
Paresthesia in extremities, numbness, tingling	0.53
Unsteady gait, walking difficulty	0.28
Weakness	0.55
Iterative fallings or equilibrium disorders	0.15
Ataxia	0.30
<b>Laboratory findings</b>	<b><i>p</i>-value<sup>†</sup></b>
Hemoglobin (g/dL)	Low sample size
Hematocrit (%)	Low sample size
Mean corpuscular volume (fL)	Low sample size
Vitamin B12 (pmol/L)	0.08
Folate (serum) (µg/L)	Low sample size
Homocysteine (µmol/L)	Low sample size
Methylmalonic acid (µmol/L)	Low sample size
<b>Main reported diagnoses</b>	<b><i>p</i>-value*</b>
Subacute combined degeneration	0.36
Generalized demyelinating polyneuropathy	0.31
Myelopathy	0.91
<b>Magnetic resonance imaging findings</b>	<b><i>p</i>-value*</b>
Presence of T2 signal hyperintensity in the spinal cord	0.17

15 \* Mann Whitney *U* test

16 † Spearman's rank correlation coefficient

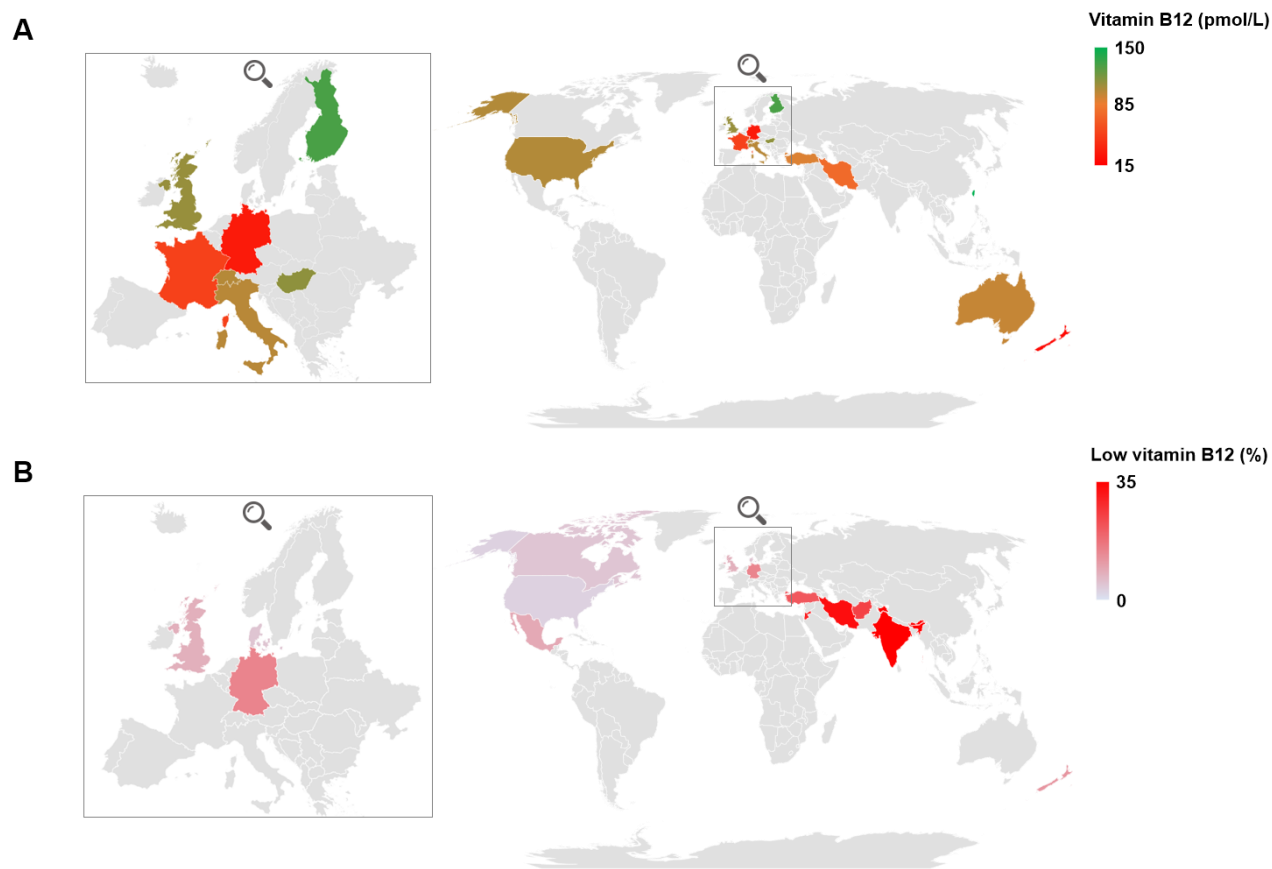
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**Figure S1.** Assessment of study bias induced by population stratification using principal component analysis. Panels (a) to (c) report the two-dimensional visualization of the whole population according to the principal components of the eigenvalue (EV) #2 vs. EV #3 (a), EV #2 vs. EV #4 (b) and EV #2 vs. EV #5 (c). Panels (d) to (f) report the three-dimensional visualization of the whole population according to the principal components for the EV #1, EV #2, and EV #3 (d), EV #2, EV #3, and EV #4 (e), and EV #3, EV #4, and EV #5 (f).

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**Figure S2.** (a) Worldwide landscape of serum or plasma vitamin B12 concentrations among patients with N<sub>2</sub>O-induced toxicity. (b) Worldwide prevalence of subjects with low serum or plasma vitamin B12 concentrations among apparently healthy individuals. Prevalence data were extracted from different studies reported around the world [133-142] and from a recently published literature review [143].



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