Elderly people accelerate the development of Alzheimer's disease / Parkinson's disease after Traumatic Head Injury in Taiwan

Alzheimer's disease 年齡分層

Rossor, Martin N., et al. "The diagnosis of young-onset dementia." *The Lancet Neurology* 9.8 (2010): 793-806. 文中將 65 歲以下定義為早發癡呆

Parkinson's disease 年齡分層

Post, Bart, et al. "Young onset Parkinson’ s disease: a modern and tailored approach." *Journal of Parkinson's disease* 10.s1 (2020): S29-S36. (Impact factor : 5.2) 提到 Parkinson’ s disease 依照發病時間分為

	Age
juvenile parkinsonism	< 20
young onset Parkinson’ s disease (YOPD)	20 – 40 (有些定義 20-50)
late onset Parkinson’ s disease (LOPD)	>50

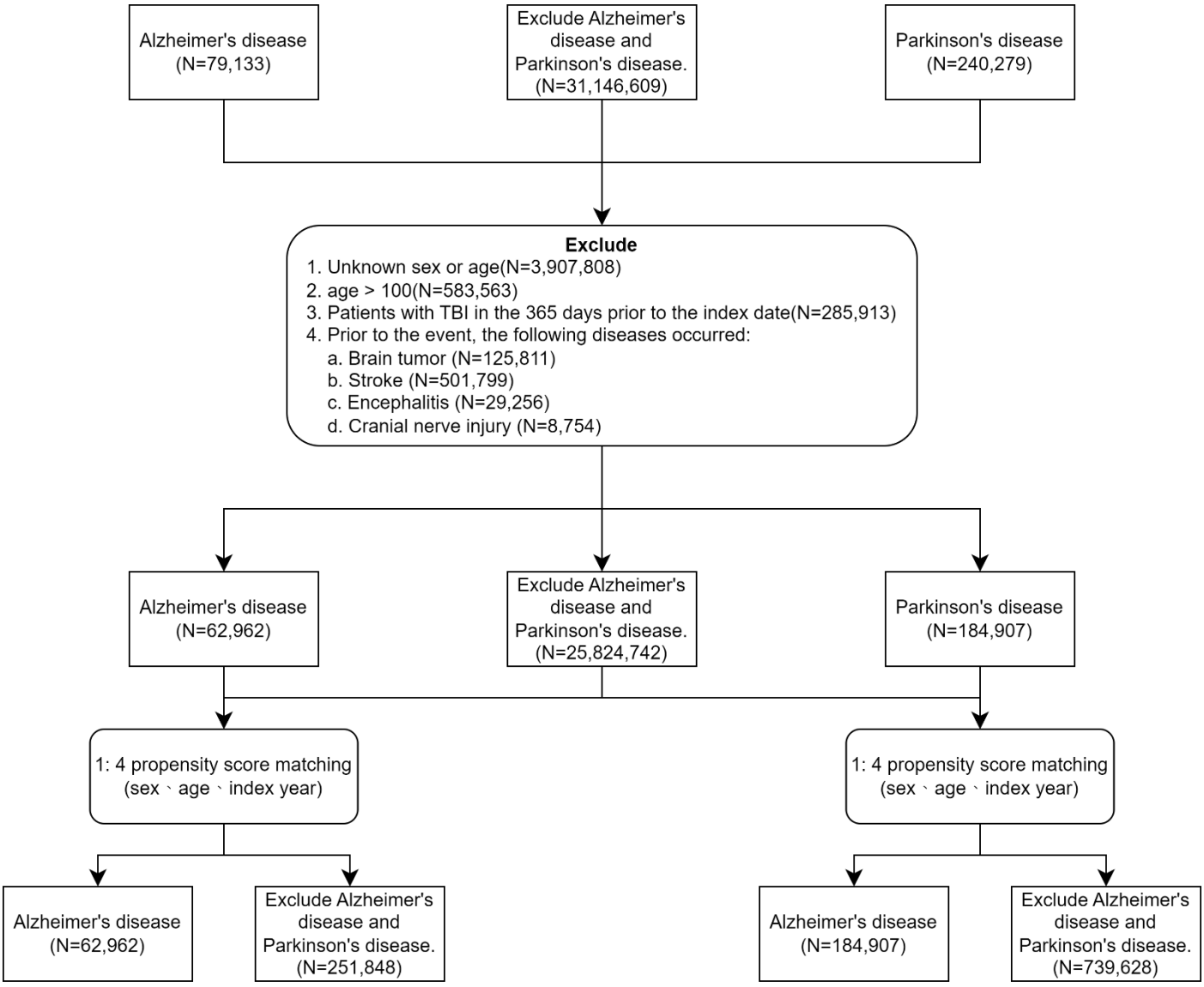
程度分類:

1. 無 TBI : 觀察時間內無任何 TBI 紀錄 : 0
2. 輕症 : 門、急診、住院(無手術、ICU) : 1
3. 重症 : 住院(有手術 或 ICU) : 2

Case-Control Study

資料區間 ：2010-2020

Figure 1. 流程圖



***無排除過往 ICU 患者(會排除掉因 TBI 有 ICU 紀錄的患者)**

***Alzheimer (一年兩次門診 一院)**

***Parkinson(一年兩次門診 一次院)**

Table 1. The baseline distribution after matching for Alzheimer's disease.

		Alzheimer(n=62962)	control(n=251848)	p.value	overall(n=314810)
ID_S				1	
	1	22708(36.07%)	90832(36.07%)		113540(36.07%)
	2	40254(63.93%)	161016(63.93%)		201270(63.93%)
index_year				1	
	2011	4193(6.66%)	16772(6.66%)		20965(6.66%)
	2012	4258(6.76%)	17032(6.76%)		21290(6.76%)
	2013	4316(6.85%)	17264(6.85%)		21580(6.85%)
	2014	4375(6.95%)	17500(6.95%)		21875(6.95%)
	2015	5094(8.09%)	20376(8.09%)		25470(8.09%)
	2016	7276(11.56%)	29104(11.56%)		36380(11.56%)
	2017	8342(13.25%)	33368(13.25%)		41710(13.25%)
	2018	8474(13.46%)	33896(13.46%)		42370(13.46%)
	2019	8784(13.95%)	35136(13.95%)		43920(13.95%)
	2020	7850(12.47%)	31400(12.47%)		39250(12.47%)
age					
	Mean(sd)	79.38(7.45)	79.38(7.45)	1	79.38(7.45)
	Median(IQR)	80(11)	80(11)	1	80(11)
	(Min,Max)	(64,100)	(64,100)		(64,100)
age_group				1	
	(60,65]	2383(3.78%)	9532(3.78%)		11915(3.78%)
	(65,70]	6316(10.03%)	25264(10.03%)		31580(10.03%)
	(70,75]	10272(16.31%)	41088(16.31%)		51360(16.31%)
	(75,80]	15188(24.12%)	60752(24.12%)		75940(24.12%)
	(80,100]	28803(45.75%)	115212(45.75%)		144015(45.75%)
AMT_group				<0.001	
	0-22800	19982(31.74%)	116585(46.29%)		136567(43.38%)
	22801-36300	23881(37.93%)	73672(29.25%)		97553(30.99%)
	36301-45800	7579(12.04%)	25557(10.15%)		33136(10.53%)
	45800~	11520(18.3%)	36034(14.31%)		47554(15.11%)
Alcohol_Use	1	18107(28.76%)	47265(18.77%)	<0.001	65372(20.77%)
Asthma	1	9797(15.56%)	25446(10.1%)	<0.001	35243(11.2%)
CVD	1	32600(51.78%)	77329(30.7%)	<0.001	109929(34.92%)
Depression	1	10277(16.32%)	11947(4.74%)	<0.001	22224(7.06%)
DM	1	22245(35.33%)	57964(23.02%)	<0.001	80209(25.48%)
Gastroesophageal_Reflux_Disease	1	13246(21.04%)	31690(12.58%)	<0.001	44936(14.27%)
Hypertension	1	43992(69.87%)	119744(47.55%)	<0.001	163736(52.01%)
Hypothyroidism	1	1580(2.51%)	3123(1.24%)	<0.001	4703(1.49%)
Peptic_Ulcer	1	22530(35.78%)	55015(21.84%)	<0.001	77545(24.63%)

資料庫中，Alzheimer 最年輕為 64 歲。

Table 2. The number of Alzheimer's disease patients with a history of TBI

		Alzheimer(n=62962)	control(n=251848)	p.value	overall(n=314810)
TBI (1-10 年發生)				<0.001	
	non-TBI	57704(91.65%)	241974(96.08%)		299678(95.19%)
	輕症	4713(7.49%)	8745(3.47%)		13458(4.27%)
	重症	545(0.87%)	1129(0.45%)		1674(0.53%)
TBI (1-3 年內發生)				<0.001	
	non-TBI	60324(95.81%)	247213(98.16%)		307537(97.69%)
	輕症	2433(3.86%)	4195(1.67%)		6628(2.11%)
	重症	205(0.33%)	440(0.17%)		645(0.2%)
TBI(3-5 年發生)				<0.001	
	non-TBI	61366(97.47%)	248848(98.81%)		310214(98.54%)
	輕症	1425(2.26%)	2676(1.06%)		4101(1.3%)
	重症	171(0.27%)	324(0.13%)		495(0.16%)
TBI (5-10 年發生)				<0.001	
	non-TBI	61420(97.55%)	248789(98.79%)		310209(98.54%)
	輕症	1370(2.18%)	2678(1.06%)		4048(1.29%)
	重症	172(0.27%)	381(0.15%)		553(0.18%)

Table 3. Adjusted odds ratios for TBI in Alzheimer's disease across different time intervals.

	TBI(1-10years)	TBI(1-3years)	TBI(3-5years)	TBI(5-10years)
non-TBI	ref.	ref.	ref.	ref.
TBI	1.6(1.54,1.66) ***	1.68(1.59,1.76) ***	1.54(1.44,1.64) ***	1.45(1.36,1.55) ***
non-TBI	ref.	ref.	ref.	ref.
輕症	1.63(1.57,1.7) ***	1.72(1.63,1.81) ***	1.55(1.45,1.66) ***	1.49(1.39,1.59) ***
重症	1.37(1.23,1.52) ***	1.29(1.09,1.53) **	1.49(1.23,1.81) ***	1.21(1,1.46) *

Table 4. The adjusted odds ratio for TBI in Alzheimer's disease across different age and time intervals.

		Age Group			
		[64,70]	(70,75]	(75,80]	(80,100]
	non-TBI	ref.	ref.	ref.	ref.
	TBI	1.62(1.45,1.8) ***	1.51(1.37,1.66) ***	1.44(1.34,1.55) ***	1.67(1.58,1.76) ***
TBI(1-10 年)	non-TBI	ref.	ref.	ref.	ref.
	輕症	1.59(1.42,1.79) ***	1.53(1.38,1.69) ***	1.48(1.37,1.6) ***	1.72(1.62,1.81) ***
	重症	1.84(1.33,2.55) ***	1.39(1.05,1.85) *	1.18(0.96,1.47)	1.3(1.12,1.52) ***
	non-TBI	ref.	ref.	ref.	ref.
	TBI	1.71(1.46,2) ***	1.63(1.43,1.86) ***	1.49(1.34,1.65) ***	1.73(1.6,1.86) ***
TBI(1-3 年)	non-TBI	ref.	ref.	ref.	ref.
	輕症	1.73(1.47,2.03) ***	1.62(1.41,1.86) ***	1.53(1.37,1.71) ***	1.79(1.66,1.93) ***
	重症	1.54(0.87,2.73)	1.76(1.13,2.75) *	1.17(0.85,1.62)	1.17(0.91,1.5)
	non-TBI	ref.	ref.	ref.	ref.
	TBI	1.59(1.31,1.93) ***	1.51(1.28,1.79) ***	1.39(1.23,1.59) ***	1.57(1.43,1.73) ***
TBI(3-5 年)	non-TBI	ref.	ref.	ref.	ref.
	輕症	1.49(1.21,1.83) ***	1.52(1.27,1.81) ***	1.42(1.24,1.62) ***	1.6(1.45,1.77) ***
	重症	2.63(1.5,4.61) ***	1.45(0.85,2.46)	1.23(0.83,1.81)	1.35(1.03,1.79) *
	non-TBI	ref.	ref.	ref.	ref.
	TBI	1.6(1.32,1.93) ***	1.3(1.1,1.55) **	1.33(1.17,1.53) ***	1.49(1.35,1.63) ***
TBI(5-10 年)	non-TBI	ref.	ref.	ref.	ref.
	輕症	1.63(1.33,1.99) ***	1.36(1.13,1.63) **	1.38(1.2,1.59) ***	1.52(1.38,1.68) ***
	重症	1.35(0.77,2.39)	0.97(0.59,1.61)	1.05(0.7,1.56)	1.26(0.97,1.63)

雖然 paper 定義 早發的痴呆是 65 歲以前，但目前資料庫最年輕為 64 所以先改用 70 做為切點。

Table 5. The adjusted odds ratio for TBI in Alzheimer's disease across different age and time intervals.

		Age Group	
		[64,70]	(70,100]
TBI(1-10 年)	non-TBI	ref.	ref.
	TBI	1.62(1.45,1.8) ***	1.61(1.55,1.67) ***
	non-TBI	ref.	ref.
	輕症	1.59(1.42,1.79) ***	1.65(1.58,1.72) ***
	重症	1.84(1.33,2.55) ***	1.32(1.18,1.48) ***
TBI(1-3 年)	non-TBI	ref.	ref.
	TBI	1.71(1.46,2) ***	1.68(1.59,1.77) ***
	non-TBI	ref.	ref.
	輕症	1.73(1.47,2.03) ***	1.73(1.63,1.83) ***
	重症	1.54(0.87,2.73)	1.27(1.06,1.52) *
TBI(3-5 年)	non-TBI	ref.	ref.
	TBI	1.59(1.31,1.93) ***	1.54(1.44,1.65) ***
	non-TBI	ref.	ref.
	輕症	1.49(1.21,1.83) ***	1.56(1.46,1.68) ***
	重症	2.63(1.5,4.61) ***	1.38(1.12,1.69) **
TBI(5-10 年)	non-TBI	ref.	ref.
	TBI	1.6(1.32,1.93) ***	1.44(1.34,1.54) ***
	non-TBI	ref.	ref.
	輕症	1.63(1.33,1.99) ***	1.48(1.37,1.59) ***
	重症	1.35(0.77,2.39)	1.19(0.97,1.45)

Table 6. The baseline distribution after matching for Parkinson's disease.

		Parkinson(n=184907)	control(n=739628)	p.value	method	overall(n=924535)
ID_S				1	chi-squared test	
	1	87724(47.44%)	350896(47.44%)			438620(47.44%)
	2	97183(52.56%)	388732(52.56%)			485915(52.56%)
index_year				1	chi-squared test	
	2011	21143(11.43%)	84572(11.43%)			105715(11.43%)
	2012	19869(10.75%)	79476(10.75%)			99345(10.75%)
	2013	19163(10.36%)	76652(10.36%)			95815(10.36%)
	2014	18479(9.99%)	73916(9.99%)			92395(9.99%)
	2015	19071(10.31%)	76284(10.31%)			95355(10.31%)
	2016	18702(10.11%)	74808(10.11%)			93510(10.11%)
	2017	17923(9.69%)	71692(9.69%)			89615(9.69%)
	2018	17586(9.51%)	70344(9.51%)			87930(9.51%)
	2019	17371(9.39%)	69484(9.39%)			86855(9.39%)
	2020	15600(8.44%)	62400(8.44%)			78000(8.44%)
age						
	Mean(sd)	71.23(14)	71.23(14)	1		71.23(14)
	Median(IQR)	74(17)	74(17)	1		74(17)
	(Min,Max)	(1,100)	(1,100)			(1,100)
age_group				1	chi-squared test	
	[0,20]	848(0.46%)	3392(0.46%)			4240(0.46%)
	(20,30]	2543(1.38%)	10172(1.38%)			12715(1.38%)
	(30,40]	4475(2.42%)	17900(2.42%)			22375(2.42%)
	(40,50]	7552(4.08%)	30208(4.08%)			37760(4.08%)
	(50,60]	17760(9.6%)	71040(9.6%)			88800(9.6%)
	(60,65]	17327(9.37%)	69308(9.37%)			86635(9.37%)
	(65,70]	22463(12.15%)	89852(12.15%)			112315(12.15%)
	(70,75]	28928(15.64%)	115712(15.64%)			144640(15.64%)
	(75,80]	33464(18.1%)	133856(18.1%)			167320(18.1%)
	(80,100]	49547(26.8%)	198188(26.8%)			247735(26.8%)
AMT_group				<0.001	chi-squared test	
	0-22800	58478(31.63%)	289441(39.13%)			347919(37.63%)
	22801-36300	68320(36.95%)	218925(29.6%)			287245(31.07%)
	36301-45800	25789(13.95%)	102248(13.82%)			128037(13.85%)
	45800~	32320(17.48%)	129014(17.44%)			161334(17.45%)
Alcohol_Use	1	53153(28.75%)	128722(17.4%)	<0.001	chi-squared test	181875(19.67%)
Asthma	1	24877(13.45%)	61001(8.25%)	<0.001	chi-squared test	85878(9.29%)
CVD	1	88432(47.83%)	186353(25.2%)	<0.001	chi-squared test	274785(29.72%)
Depression	1	35466(19.18%)	31689(4.28%)	<0.001	chi-squared test	67155(7.26%)
DM	1	59392(32.12%)	150302(20.32%)	<0.001	chi-squared test	209694(22.68%)
Gastroesophageal_Reflux_Disease	1	37735(20.41%)	82670(11.18%)	<0.001	chi-squared test	120405(13.02%)
Hypertension	1	116835(63.19%)	304307(41.14%)	<0.001	chi-squared test	421142(45.55%)
Hypothyroidism	1	4029(2.18%)	7916(1.07%)	<0.001	chi-squared test	11945(1.29%)
Peptic_Ulcer	1	62637(33.87%)	142501(19.27%)	<0.001	chi-squared test	205138(22.19%)

Table 7. The number of Parkinson's disease patients with a history of TBI

		Parkinson(n=184907)	control(n=739628)	p.value	overall(n=924535)
TBI (1-10 年內發生)				<0.001	
	non-TBI	173553(93.86%)	717794(97.05%)		891347(96.41%)
	輕症	10139(5.48%)	19439(2.63%)		29578(3.2%)
	重症	1215(0.66%)	2395(0.32%)		3610(0.39%)
TBI (1-3 年內發生)				<0.001	
	non-TBI	178578(96.58%)	728666(98.52%)		907244(98.13%)
	輕症	5756(3.11%)	9908(1.34%)		15664(1.69%)
	重症	573(0.31%)	1054(0.14%)		1627(0.18%)
TBI(3-5 年發生)				<0.001	
	non-TBI	181508(98.16%)	733020(99.11%)		914528(98.92%)
	輕症	3045(1.65%)	5935(0.8%)		8980(0.97%)
	重症	354(0.19%)	673(0.09%)		1027(0.11%)
TBI (5-10 年發生)				<0.001	
	non-TBI	182152(98.51%)	733718(99.2%)		915870(99.06%)
	輕症	2456(1.33%)	5217(0.71%)		7673(0.83%)
	重症	299(0.16%)	693(0.09%)		992(0.11%)

Table 8. Adjusted odds ratios for TBI in Parkinson's disease across different time intervals.

	TBI(1-10years)	TBI(1-3years)	TBI(3-5years)	TBI(5-10years)
non-TBI	ref.	ref.	ref.	ref.
TBI	1.5(1.47,1.54) ***	1.65(1.59,1.7) ***	1.44(1.38,1.51) ***	1.29(1.23,1.35) ***
non-TBI	ref.	ref.	ref.	ref.
輕症	1.53(1.49,1.57) ***	1.68(1.62,1.74) ***	1.45(1.38,1.52) ***	1.31(1.25,1.38) ***
重症	1.33(1.24,1.43) ***	1.37(1.23,1.53) ***	1.39(1.21,1.59) ***	1.12(0.97,1.29)

因早發的 Parkinson's disease 定義有兩種。年齡 ：20-40 / 20-50，因此分兩種方式進行評估。

Table 9. The adjusted odds ratio for TBI in Parkinson's disease across different age and time intervals.

		Age Group				
		[1,20]	(20,40]	(40,50]	(50,70]	(70,100]
	non-TBI	ref.	ref.	ref.	ref.	ref.
	TBI	1.64(1,2.69) *	1.53(1.3,1.8) ***	1.63(1.39,1.91) ***	1.45(1.38,1.53) ***	1.49(1.45,1.54) ***
TBI(1-10 年)	non-TBI	ref.	ref.	ref.	ref.	ref.
	輕症	1.69(1.02,2.8) *	1.49(1.25,1.76) ***	1.52(1.29,1.8) ***	1.45(1.38,1.53) ***	1.54(1.49,1.59) ***
	重症	1.09(0.14,8.83)	2.37(1.23,4.57) **	3.68(2.07,6.54) ***	1.5(1.29,1.75) ***	1.21(1.11,1.32) ***
	non-TBI	ref.	ref.	ref.	ref.	ref.
	TBI	1.7(0.88,3.3)	1.33(1.05,1.69) *	1.83(1.46,2.29) ***	1.6(1.5,1.72) ***	1.64(1.57,1.7) ***
TBI(1-3 年)	non-TBI	ref.	ref.	ref.	ref.	ref.
	輕症	1.76(0.88,3.53)	1.28(1,1.64) *	1.71(1.35,2.16) ***	1.61(1.5,1.73) ***	1.69(1.62,1.76) ***
	重症	1.23(0.14,10.61)	2.43(0.95,6.18)	3.6(1.72,7.52) ***	1.52(1.21,1.92) ***	1.24(1.09,1.4) **
	non-TBI	ref.	ref.	ref.	ref.	ref.
	TBI	2.76(1.12,6.76) *	1.91(1.45,2.52) ***	1.61(1.21,2.14) **	1.5(1.38,1.64) ***	1.37(1.3,1.45) ***
TBI(3-5 年)	non-TBI	ref.	ref.	ref.	ref.	ref.
	輕症	2.89(1.17,7.15) *	1.86(1.39,2.47) ***	1.6(1.19,2.14) **	1.47(1.34,1.61) ***	1.39(1.31,1.47) ***
	重症	0(0,Inf)	3.09(1.04,9.21) *	2(0.5,8.01)	1.87(1.43,2.45) ***	1.23(1.04,1.44) *
	non-TBI	ref.	ref.	ref.	ref.	ref.
	TBI	1.18(0.44,3.13)	1.65(1.22,2.22) **	1.42(1.05,1.91) *	1.23(1.12,1.35) ***	1.27(1.19,1.35) ***
TBI(5-10 年)	non-TBI	ref.	ref.	ref.	ref.	ref.
	輕症	1.18(0.44,3.13)	1.67(1.23,2.26) ***	1.29(0.95,1.77)	1.25(1.13,1.37) ***	1.3(1.22,1.39) ***
	重症	NA	1.16(0.23,5.9)	6.46(1.61,25.91) **	1.09(0.81,1.47)	1.06(0.9,1.26)

Table 10. The adjusted odds ratio for TBI in Parkinson's disease across different age and time intervals.

		Age Group			
		[1,20]	(20,50]	(50,70]	(70,100]
	non-TBI	ref.	ref.	ref.	ref.
	TBI	1.64(1,2.69) *	1.59(1.42,1.78) ***	1.45(1.38,1.53) ***	1.49(1.45,1.54) ***
TBI(1-10 年)	non-TBI	ref.	ref.	ref.	ref.
	輕症	1.69(1.02,2.8) *	1.52(1.35,1.71) ***	1.45(1.38,1.53) ***	1.54(1.49,1.59) ***
	重症	1.09(0.14,8.83)	3.02(1.97,4.62) ***	1.5(1.29,1.75) ***	1.21(1.11,1.32) ***
	non-TBI	ref.	ref.	ref.	ref.
	TBI	1.7(0.88,3.3)	1.59(1.36,1.87) ***	1.6(1.5,1.72) ***	1.64(1.57,1.7) ***
TBI(1-3 年)	non-TBI	ref.	ref.	ref.	ref.
	輕症	1.76(0.88,3.53)	1.51(1.28,1.79) ***	1.61(1.5,1.73) ***	1.69(1.62,1.76) ***
	重症	1.23(0.14,10.61)	3.02(1.7,5.37) ***	1.52(1.21,1.92) ***	1.24(1.09,1.4) **
	non-TBI	ref.	ref.	ref.	ref.
	TBI	2.76(1.12,6.76) *	1.78(1.46,2.16) ***	1.5(1.38,1.64) ***	1.37(1.3,1.45) ***
TBI(3-5 年)	non-TBI	ref.	ref.	ref.	ref.
	輕症	2.89(1.17,7.15) *	1.74(1.42,2.13) ***	1.47(1.34,1.61) ***	1.39(1.31,1.47) ***
	重症	0(0,Inf)	2.67(1.15,6.19) *	1.87(1.43,2.45) ***	1.23(1.04,1.44) *
	non-TBI	ref.	ref.	ref.	ref.
	TBI	1.18(0.44,3.13)	1.54(1.24,1.9) ***	1.23(1.12,1.35) ***	1.27(1.19,1.35) ***
TBI(5-10 年)	non-TBI	ref.	ref.	ref.	ref.
	輕症	1.18(0.44,3.13)	1.48(1.19,1.84) ***	1.25(1.13,1.37) ***	1.3(1.22,1.39) ***
	重症	NA	3.26(1.22,8.71) *	1.09(0.81,1.47)	1.06(0.9,1.26)

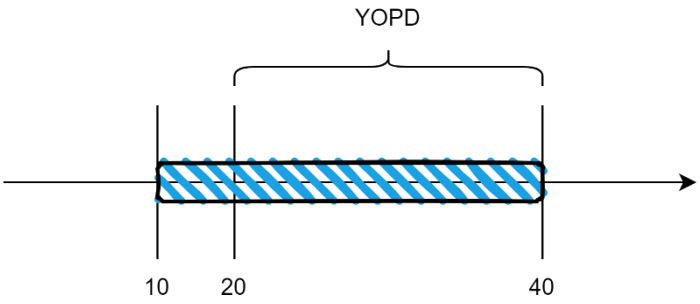
忘記要將 50 歲以上合併，但初步看起來 YOPD 的 odds ratio 都高於 年齡 (50,70]、(70,100] 兩組。

Cohort study

程度分類:

1. 無 TBI：觀察時間內無任何 TBI 紀錄 ：0
2. 輕症 ：門、急診、住院(無手術、ICU) : 1
3. 重症 ： 住院(有手術 或 ICU) : 2

分析方法: 參考 Osler, Merete, et al. "Traumatic brain injury and risk of dementia at different levels of cognitive ability and education." *European journal of neurology* 27.2 (2020): 399-405.



以 YOPD (Age : 20-40) 為例，我們資料最長追蹤 10 年，因此最小為 10 歲開始追蹤，10 年後有機會發生 YOPD，且沒有在 20 以前發生 PD。排除 40 歲以上患者，因不可能發生 YOPD。當患者超過 40 歲後做為 censored。

統整後續分析各群的限制如下 ：

		年齡區間	Censored 年齡	幾歲前無 TBI
整體比較	AD	50~ (因最早發病年齡為 64，因此更精確要用 54~)	-	-
以 65 歲做為早發 Alzheimer's disease	YOAD_1	50~65 (因最早發病年齡為 64，因此更精確要用 54~65)	65	-
	LOAD_1	55~	-	65
以 70 歲做為早發 Alzheimer's disease	YOAD_2	50~70 (因最早發病年齡為 64，因此更精確要用 54~70)	70	-
	LOAD_2	60~	-	70
Parkinson's disease	PD	-	-	-
以 20-40 歲做為早發 Parkinson's disease	YOPD_1	10~40	40	20
以 20-50 歲做為早發 Parkinson's disease	YOPD_2	10~50	50	20
50 歲以上 Parkinson's disease	LOPD	40~	-	50

“- “: 表示無限制

Figure 2. Alzheimer 流程圖

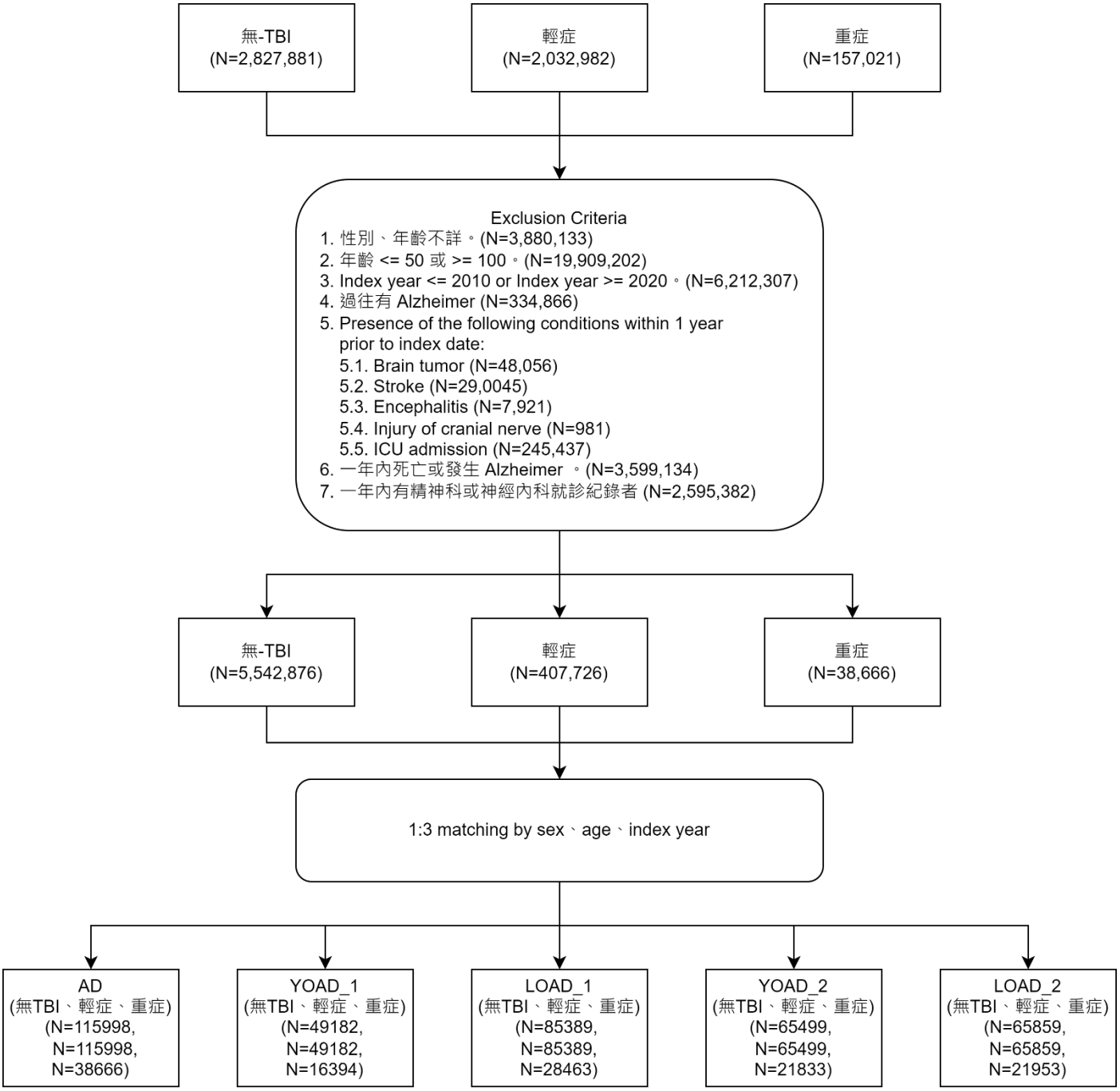


Figure 3. Parkinson 流程圖

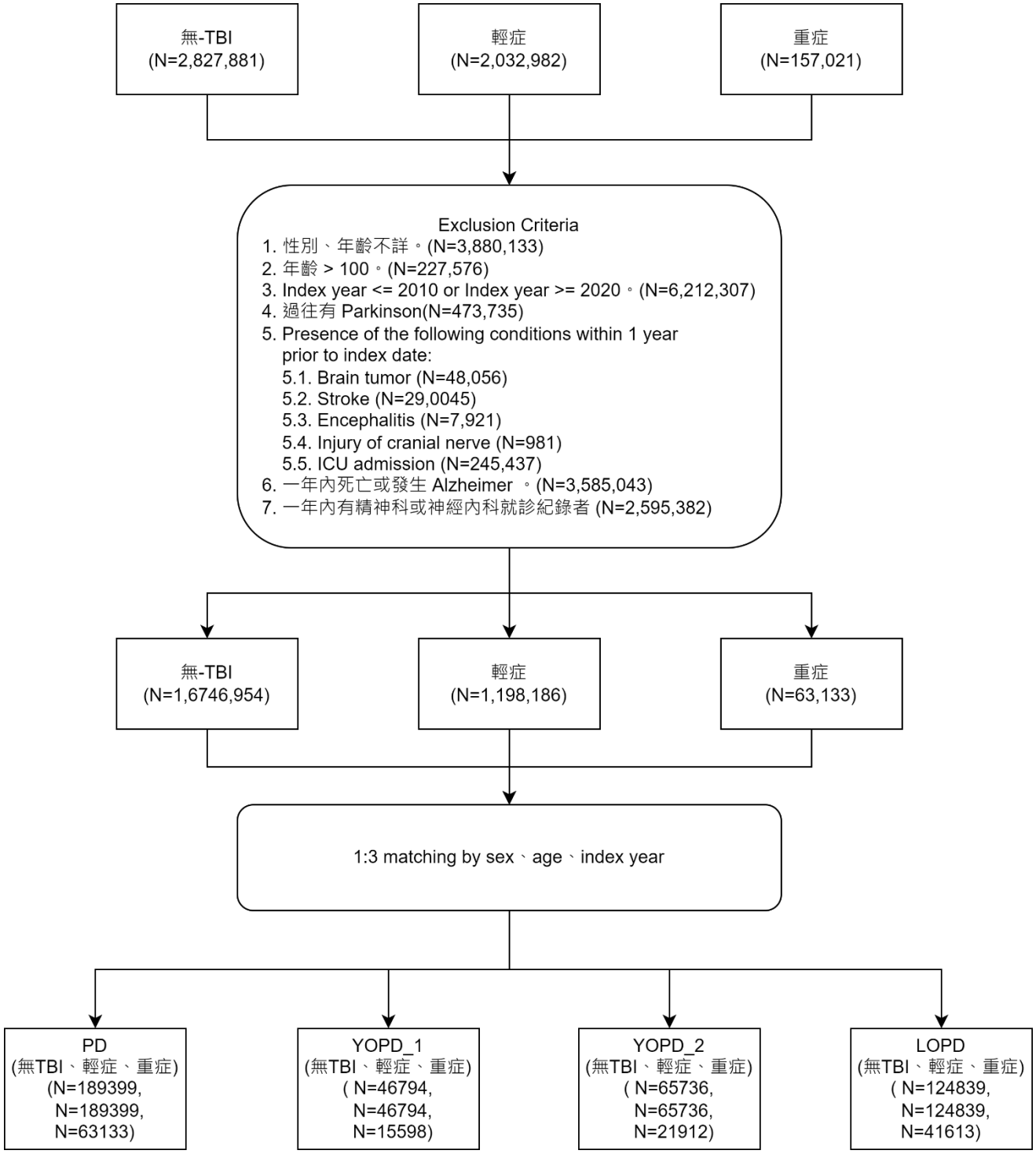


Table 11. Alzheimer's disease 配對前基線分布

		無 TBI (n=5542876)	輕症 (n=407726)	重症 (n=38666)	p.value	overall(n=5989268)
ID_S					<0.001	
	1	2861705(51.63%)	208379(51.11%)	22617(58.49%)		3092701(51.64%)
	2	2681171(48.37%)	199347(48.89%)	16049(41.51%)		2896567(48.36%)
index_year					<0.001	
	2011	594430(10.72%)	27727(6.8%)	3825(9.89%)		625982(10.45%)
	2012	593780(10.71%)	27692(6.79%)	3671(9.49%)		625143(10.44%)
	2013	596442(10.76%)	25732(6.31%)	3933(10.17%)		626107(10.45%)
	2014	604146(10.9%)	25574(6.27%)	4024(10.41%)		633744(10.58%)
	2015	612174(11.04%)	25041(6.14%)	4001(10.35%)		641216(10.71%)
	2016	620863(11.2%)	79338(19.46%)	4738(12.25%)		704939(11.77%)
	2017	629547(11.36%)	67530(16.56%)	4915(12.71%)		701992(11.72%)
	2018	639791(11.54%)	65091(15.96%)	4852(12.55%)		709734(11.85%)
	2019	651703(11.76%)	64001(15.7%)	4707(12.17%)		720411(12.03%)
age						
	Mean(sd)	65.61(12.5)	65.71(10.87)	68.54(10.91)	<0.001	65.64(12.39)
	Median(IQR)	62.07(17.52)	63.65(16.53)	67.59(17.32)	<0.001	62.21(17.49)
	(Min,Max)	(50.01,99.99)	(50.01,99.99)	(50.01,99.9)		(50.01,99.99)
age_group						
	(50,60]	2358883(42.56%)	150951(37.02%)	10145(26.24%)		2519979(42.07%)
	(60,65]	917874(16.56%)	70884(17.39%)	6256(16.18%)		995014(16.61%)
	(65,70]	603510(10.89%)	55885(13.71%)	5440(14.07%)		664835(11.1%)
	(70,75]	421465(7.6%)	41431(10.16%)	5128(13.26%)		468024(7.81%)
	(75,80]	350390(6.32%)	36153(8.87%)	4916(12.71%)		391459(6.54%)
	(80,100]	890754(16.07%)	52422(12.86%)	6781(17.54%)		949957(15.86%)
AMT_group					<0.001	
	15840-22800	1671347(30.15%)	74232(18.21%)	9078(23.48%)		1754657(29.3%)
	22801-36300	1588683(28.66%)	161740(39.67%)	16142(41.75%)		1766565(29.5%)
	36301-45800	1147206(20.7%)	92279(22.63%)	7028(18.18%)		1246513(20.81%)
	45800~	1135640(20.49%)	79475(19.49%)	6418(16.6%)		1221533(20.4%)
Alcohol_Use	1	186377(3.36%)	18385(4.51%)	2168(5.61%)	<0.001	206930(3.46%)
Asthma	1	144367(2.6%)	20853(5.11%)	1876(4.85%)	<0.001	167096(2.79%)
CVD	1	533931(9.63%)	66351(16.27%)	8308(21.49%)	<0.001	608590(10.16%)
Depression	1	28882(0.52%)	4625(1.13%)	687(1.78%)	<0.001	34194(0.57%)
DM	1	699779(12.62%)	82786(20.3%)	9101(23.54%)	<0.001	791666(13.22%)
Gastroesophageal_Reflux_Disease	1	202994(3.66%)	25005(6.13%)	1883(4.87%)	<0.001	229882(3.84%)
Hypertension	1	1407665(25.4%)	154501(37.89%)	16578(42.87%)	<0.001	1578744(26.36%)
Hypothyroidism	1	26790(0.48%)	2883(0.71%)	244(0.63%)	<0.001	29917(0.5%)
Peptic_Ulcer	1	257243(4.64%)	28654(7.03%)	2986(7.72%)	<0.001	288883(4.82%)

Table 12. Parkinson's disease 配對前基線分布

		無 TBI (n=16746954)	輕症 (n=1198186)	重症 (n=63133)	p.value	overall(n=18008273)
ID_S					<0.001	
	1	8456905(50.5%)	695470(58.04%)	39915(63.22%)		9192290(51.04%)
	2	8290049(49.5%)	502716(41.96%)	23218(36.78%)		8815983(48.96%)
index_year					<0.001	
	2011	1861964(11.12%)	88839(7.41%)	6772(10.73%)		1957575(10.87%)
	2012	1849205(11.04%)	84545(7.06%)	6047(9.58%)		1939797(10.77%)
	2013	1832604(10.94%)	76506(6.39%)	6336(10.04%)		1915446(10.64%)
	2014	1829006(10.92%)	73513(6.14%)	6325(10.02%)		1908844(10.6%)
	2015	1833186(10.95%)	69663(5.81%)	6231(9.87%)		1909080(10.6%)
	2016	1841797(11%)	228995(19.11%)	7994(12.66%)		2078786(11.54%)
	2017	1859152(11.1%)	201002(16.78%)	8092(12.82%)		2068246(11.48%)
	2018	1889872(11.28%)	191491(15.98%)	7807(12.37%)		2089170(11.6%)
	2019	1950168(11.64%)	183632(15.33%)	7529(11.93%)		2141329(11.89%)
age						
	Mean(sd)	39.59(22.88)	37.41(24.16)	52.63(22.7)	<0.001	39.49(22.99)
	Median(IQR)	38.82(33.58)	35.4(39.01)	56.84(36.15)	<0.001	38.7(34.09)
	(Min,Max)	(0.01,99.99)	(0.01,99.99)	(0.02,99.9)		(0.01,99.99)
age_group					<0.001	
	[0,20]	3777611(22.56%)	351876(29.37%)	7106(11.26%)		4136593(22.97%)
	(20,30]	2236262(13.35%)	172079(14.36%)	6423(10.17%)		2414764(13.41%)
	(30,40]	2672202(15.96%)	139548(11.65%)	5259(8.33%)		2817009(15.64%)
	(40,50]	2534343(15.13%)	130456(10.89%)	6321(10.01%)		2671120(14.83%)
	(50,60]	2357494(14.08%)	150760(12.58%)	10118(16.03%)		2518372(13.98%)
	(60,65]	916535(5.47%)	70648(5.9%)	6222(9.86%)		993405(5.52%)
	(65,70]	601915(3.59%)	55591(4.64%)	5369(8.5%)		662875(3.68%)
	(70,75]	419327(2.5%)	40979(3.42%)	5008(7.93%)		465314(2.58%)
	(75,80]	347301(2.07%)	35431(2.96%)	4765(7.55%)		387497(2.15%)
	(80,100]	883964(5.28%)	50818(4.24%)	6542(10.36%)		941324(5.23%)
AMT_group					<0.001	
	15840-22800	2673983(15.97%)	140332(11.71%)	12351(19.56%)		2826666(15.7%)
	22801-36300	6322151(37.75%)	543447(45.36%)	29082(46.06%)		6894680(38.29%)
	36301-45800	3046569(18.19%)	225267(18.8%)	10908(17.28%)		3282744(18.23%)
	45800~	4704251(28.09%)	289140(24.13%)	10792(17.09%)		5004183(27.79%)
Alcohol_Use	1	417341(2.49%)	36036(3.01%)	2914(4.62%)	<0.001	456291(2.53%)
Asthma	1	395000(2.36%)	50214(4.19%)	2194(3.48%)	<0.001	447408(2.48%)
CVD	1	624018(3.73%)	73160(6.11%)	8517(13.49%)	<0.001	705695(3.92%)
Depression	1	54837(0.33%)	7960(0.66%)	863(1.37%)	<0.001	63660(0.35%)
DM	1	831940(4.97%)	92439(7.71%)	9498(15.04%)	<0.001	933877(5.19%)
Gastroesophageal_Reflux_Disease	1	349644(2.09%)	37632(3.14%)	2259(3.58%)	<0.001	389535(2.16%)
Hypertension	1	1666695(9.95%)	170224(14.21%)	17198(27.24%)	<0.001	1854117(10.3%)
Hypothyroidism	1	47338(0.28%)	4146(0.35%)	272(0.43%)	<0.001	51756(0.29%)
Peptic_Ulcer	1	386827(2.31%)	38807(3.24%)	3341(5.29%)	<0.001	428975(2.38%)

Table 13. 配對後的 Incidence rate

	level	n	TBI AGE [min, max]	Event AGE [min, max]	Event	Total person years	Incidence rate (Per 1000 person-years)
AD	無 TBI	115998	[50.01,99.99]	[51.08,109.2]	673	552173.699	1.219
	輕症	115998	[50.01,99.99]	[51.08,107.03]	1103	549981.762	2.006
	重症	38666	[50.01,99.9]	[51.16,108.03]	312	177087.773	1.762
YOAD_1	無 TBI	49182	[50.01,64.99]	[51.08,65]	11	195159.474	0.056
	輕症	49182	[50.01,64.99]	[51.08,65]	10	193984.249	0.052
	重症	16394	[50.01,64.99]	[51.16,65]	9	62873.644	0.143
LOAD_1	無 TBI	85389	[55.05,99.99]	[65.01,109.2]	660	416805.934	1.583
	輕症	85389	[55.01,99.99]	[65.01,107.03]	1095	414514.751	2.642
	重症	28463	[55.19,99.9]	[65.01,108.03]	303	133584.474	2.268
YOAD_2	無 TBI	65499	[50.01,69.99]	[51.08,70]	67	282857.512	0.237
	輕症	65499	[50.01,69.99]	[51.08,70]	86	282581.230	0.304
	重症	21833	[50.01,69.99]	[51.16,70]	29	91605.216	0.317
LOAD_2	無 TBI	65859	[60.01,99.99]	[70.01,109.2]	602	319251.340	1.886
	輕症	65859	[60.01,99.99]	[70.01,107.03]	1011	316616.504	3.193
	重症	21953	[60.11,99.9]	[70.01,108.03]	283	101962.721	2.776
PD	無 TBI	189399	[0.01,99.99]	[1.05,109.2]	1258	941882.592	1.336
	輕症	189399	[0.05,99.99]	[1.38,107.03]	2097	937509.515	2.237
	重症	63133	[0.02,99.9]	[1.13,108.03]	794	304640.178	2.606
YOPD_1	無 TBI	46794	[10.15,39.99]	[20.06,40]	6	228672.956	0.026
	輕症	46794	[10.17,39.99]	[20.06,40]	13	229736.244	0.057
	重症	15598	[10.72,39.99]	[20.05,40]	18	75540.452	0.238
YOPD_2	無 TBI	65736	[10.15,49.99]	[20.06,50]	13	323698.271	0.040
	輕症	65736	[10.17,49.99]	[20.06,50]	28	322181.644	0.087
	重症	21912	[10.72,49.99]	[20.05,50]	35	105517.786	0.332
LOPD	無 TBI	124839	[40.12,99.99]	[50.01,109.2]	1245	612993.071	2.031
	輕症	124839	[40.15,99.99]	[50.04,107.03]	2071	609192.819	3.400
	重症	41613	[40.1,99.9]	[50.02,108.03]	756	196547.611	3.846

Table 13. Alzheimer's disease HR

	AD	YOAD_1	LOAD_1	YOAD_2	LOAD_2
無 TBI	**Ref.**	**Ref.**	**Ref.**	**Ref.**	**Ref.**
TBI	1.58(1.44,1.74) ***	1.38(0.59,3.22)	1.61(1.46,1.77) ***	1.25(0.91,1.72)	1.63(1.47,1.8) ***
無 TBI	**Ref.**	**Ref.**	**Ref.**	**Ref.**	**Ref.**
輕症	1.61(1.46,1.78) ***	0.98(0.37,2.6)	1.65(1.49,1.82) ***	1.21(0.86,1.71)	1.66(1.5,1.85) ***
重症	1.49(1.3,1.71) ***	2.41(0.87,6.64)	1.47(1.28,1.7) ***	1.36(0.86,2.13)	1.51(1.31,1.75) ***

Table 14. Parkinson's disease HR

	PD	YOPD_1	YOPD_2	LOPD
無 TBI	**Ref.**	**Ref.**	**Ref.**	**Ref.**
TBI	1.74(1.62,1.86) ***	4.19(1.72,10.18) **	3.58(1.95,6.59) ***	1.72(1.6,1.84) ***
無 TBI	**Ref.**	**Ref.**	**Ref.**	**Ref.**
輕症	1.65(1.54,1.78) ***	2.47(0.93,6.55)	2(1.01,3.94) *	1.65(1.53,1.77) ***
重症	2.01(1.83,2.2) ***	8.56(3.3,22.18) ***	8.6(4.4,16.8) ***	1.93(1.76,2.12) ***