

Supplementary material

The lists of clinical codes curated by the MULTIPLY project were used to establish instances of the conditions of interest(1). The primary care codelists for depression and anxiety were amended by psychiatrists within the LINC team. Dyslipidemia is not defined within the MULTIPLY clinical code lists, therefore the clinical code list from Baksh *et al.* was used to identify instances of dyslipidemia within primary care records(2), and ICD-10 codes E78.0, E78.1, E78.2, E78.3, E78.4, E78.5, E88.81 were used to define dyslipidemia in HES.

Trait	GWAS
MDD	Wray <i>et al.</i> , 2018 (UKBB removed) (3)
Anxiety	Meier <i>et al.</i> , 2019 (4)
LDL	Willer <i>et al.</i> , 2013 (5)
SBP	Keaton <i>et al.</i> , 2024 (6) (only ICBP)
BMI	Locke <i>et al.</i> 2015 (7)
T2D	Mahajan <i>et al.</i> , 2018 (UKBB removed) (8)
CKD	Pattaro <i>et al.</i> , 2016 (9)

Supplementary Table 1. Genome-wide association studies used for polygenic risk score generation.

CNV	Count
Any	7,549
1p36 del	1
TAR del	80
TAR dup	463
1q21.1 del	119
1q21.1 dup	193
NRXN1 del	176
2q11.2 del	34
2q13 del	56
2q13 dup	73
2q37 del	1
3q29 del	9
WH dup	3
WBS del	1

WBS dup	16
<i>8p23.1 del</i>	4
8p23.1 dup	8
<i>EMHT1 dup</i>	1
<i>10q23 del</i>	3
15q11.2 del	1,748
15q11.2 dup	2,284
<i>PWS del</i>	1
PWS dup	19
15q13.3 del	47
<i>15q24 del</i>	1
15q24 dup	9
<i>15q25 del</i>	1
16p13.11 del	140
16p13.11 dup	888
16p12.1 del	260
16p11.2distal del	62
16p11.2distal dup	142
16p11.2 del	123
16p11.2 dup	142
17p13.3 YWHAE del	27
17p13.3 YWHAE dup	8
<i>17p13.3 PAFAH1B1 del</i>	1
<i>17p13.3 PAFAH1B1 dup</i>	3
<i>SMS</i>	2
Potocki Lupski	6
17q11.2 delNF1	10
17q11.2 dup NF1	3
17q12 del	9
17q12 dup	104
22q11.2 del	10
22q11.2 dup	294
22q11.2 distal del	5
22q11.2 distal dup	14

Supplementary Table 2. Number of individuals with each ND-CNV. ND-CNVs that appeared less than five times are in italics.

	ND-CNV	No ND-CNV
Age at recruitment (Mean (min, max))	56.07 (40,70)	56.55 (37,73)
Townsend deprivation index (Mean (min, max))	-0.86 (-6.26, 10.56)	-1.32 (-6.26, 11.00)
Female (N (%))	3,934 (52.11)	245,589 (54.32)

Supplementary Table 3. Demographic characteristics of individuals with and without a ND-CNV. NV. Townsend deprivation index is measure of socioeconomic deprivation, with higher value indicating a more deprived environment.

	ND-CNV (N=7,546)		No ND-CNV (N=451,937)	
	Cases	Frequency (%)	Cases	Frequency (%)
Anxiety	878	11.6	42,365	9.4
Depression	1,335	17.7	65,040	14.4
Somatoform disorder	161	2.1	8,513	1.9
Any internalising disorder	1,685	22.3	84,755	18.8
Hypertension	2,765	36.6	153,829	34.0
Obesity	975	12.9	46,176	10.2
Chronic kidney disease	570	7.6	26,924	6.0
Type II diabetes	870	11.5	39,236	8.7
Dyslipidemia	1,709	22.6	95,960	21.2
Any CM	3,705	49.1	206,240	45.7

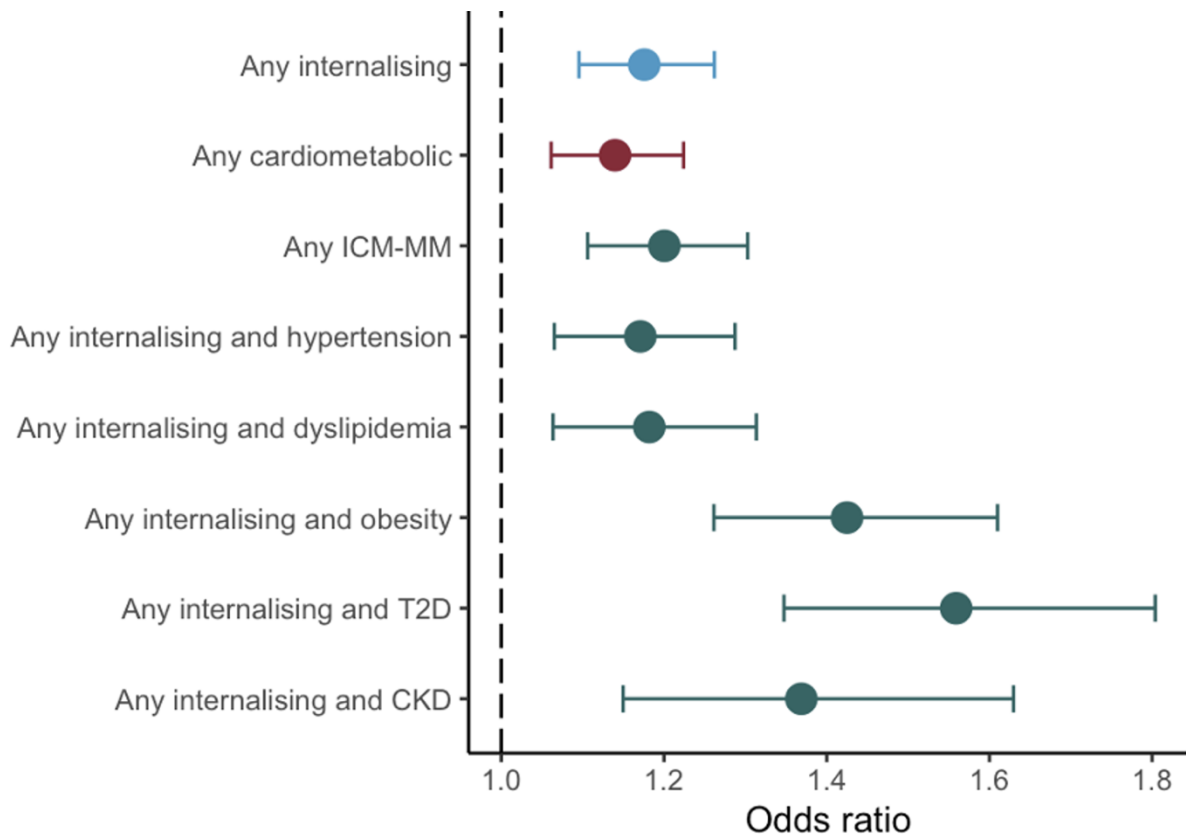
Supplementary Table 4. Counts and frequency for each of the conditions of interest in individuals with and without a ND-CNV.

	OR (CI)	p-value
Anxiety	1.25 (1.16-1.34)	9.16x10 ⁻¹⁰
Depression	1.24 (1.16-1.31)	5.11x10 ⁻¹²
Somatoform disorder	1.13 (0.96-1.32)	0.144
Any internalising condition	1.22 (1.15 -1.28)	4.50x10 ⁻¹²
Hypertension	1.16 (1.10-1.22)	1.20x10 ⁻⁸
Obesity	1.27 (1.18-1.36)	1.04x10 ⁻¹¹
Chronic kidney disease	1.10 (1.22-1.46)	1.69x10 ⁻³
Type II diabetes	1.37 (1.27-1.48)	2.43x10 ⁻¹⁷
Dyslipidaemia	1.33 (1.03-1.16)	1.45x10 ⁻¹⁰
Any cardiometabolic condition	1.19 (1.13-1.24)	5.37x10 ⁻¹²
Any internalising and hypertension	1.21 (1.13-1.31)	5.55x10 ⁻⁷
Any internalising and dyslipidemia	1.27 (1.16-1.38)	1.34x10 ⁻⁷
Any internalising and obesity	1.48 (1.33-.164)	1.51x10 ⁻¹³
Any internalising T2D	1.57 (1.38-1.77)	1.66x10 ⁻⁶
Any internalising and CKD	1.44 (1.24-1.66)	1.09x10 ⁻⁶
Any ICM-MM	1.25 (1.17-1.34)	3.14x10 ⁻¹¹

Supplementary Table 5. Association of individual conditions and ICM-MM phenotypes with the presence of a ND-CNV.

	OR (CI)	p-value
Any ICM-MM	1.18 (1.10-1.26)	1.32x10 ⁻⁶
Any internalising and hypertension	1.14 (1.05-1.23)	9.56x10 ⁻⁴
Any internalising and dyslipidemia	1.20 (1.10-1.32)	3.89x10 ⁻⁵
Any internalising T2D	1.41 (1.24-1.60)	7.11x10 ⁻⁸
Any internalising and CKD	1.35 (1.17-1.56)	6.53x10 ⁻⁵

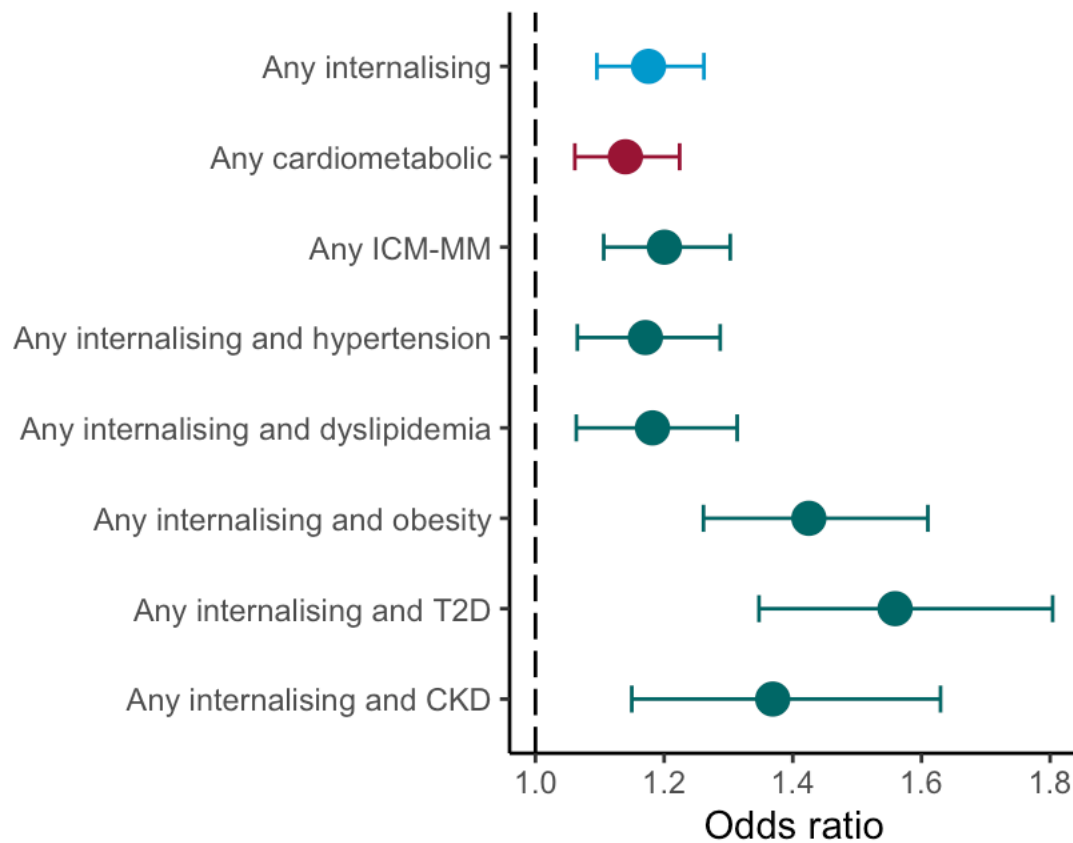
Supplementary Table 6. Association of ICM-MM phenotypes with the presence of a ND-CNV adjusting for BMI. Obesity was not included as an outcome in this analysis.



Supplementary Figure 1. Association of ND-CNVs with multimorbidity for individuals with both primary care and HES data (N= 229,951).

	OR (CI)	p-value
Any ICM-MM	1.20 (1.11-1.30)	1.21x10 ⁻⁵
Any internalising and hypertension	1.17 (1.07-1.29)	1.09x10 ⁻³
Any internalising and dyslipidemia	1.18 (1.06-1.31)	1.92x10 ⁻³
Any internalising and obesity	1.48 (1.26-1.61)	1.30x10 ⁻⁸
Any internalising T2D	1.37 (1.35-1.80)	2.42x10 ⁻⁹
Any internalising and CKD	1.56 (1.15-1.63)	4.20x10 ⁻⁴

Supplementary Table 7. Association of ICM-MM phenotypes with the presence of a ND-CNV for individuals with both primary care and HES data (N= 229,951).



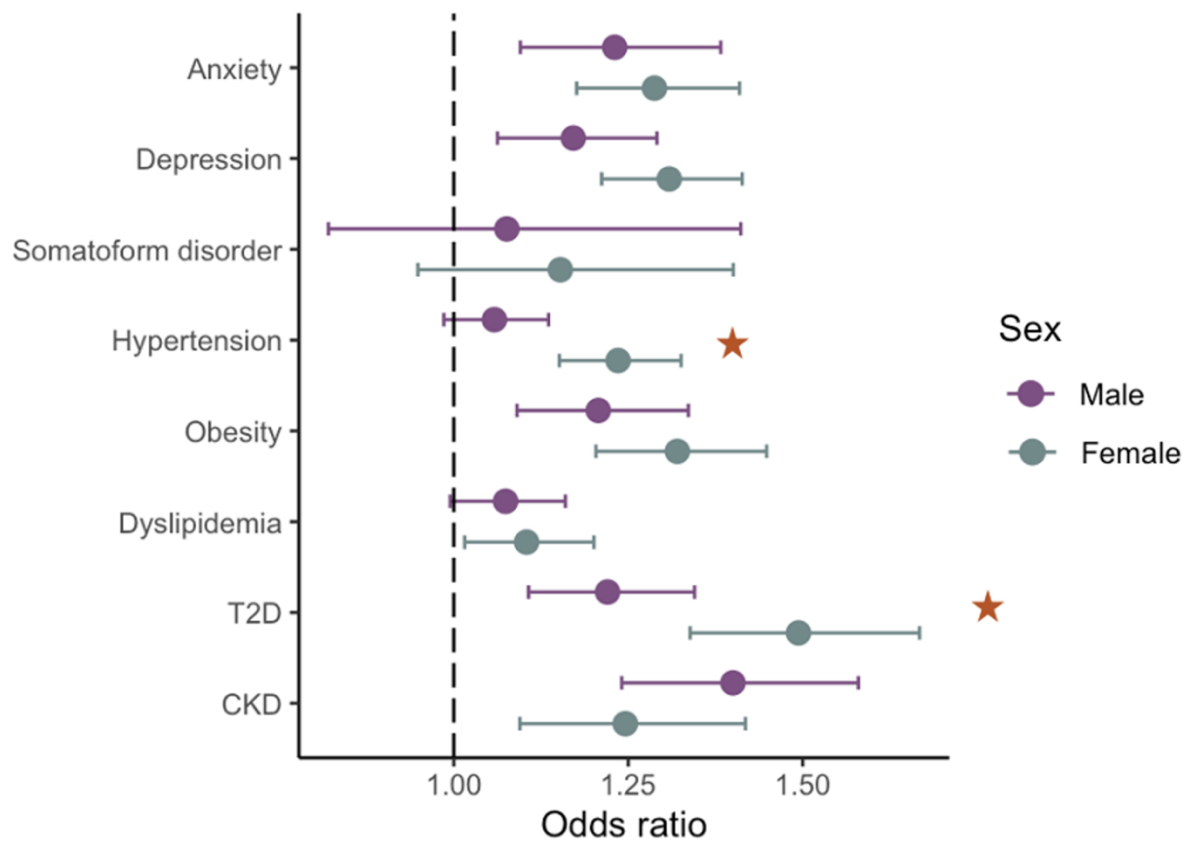
Supplementary Figure 2. Association of ND-CNVs with multimorbidity excluding individuals with 16p11.2 proximal and distal deletions (N= 185).

	OR (CI)	p-value
Any ICM-MM	1.20 (1.11-1.30)	2.08x10 ⁻⁹
Any internalising and hypertension	1.17(1.07-1.29)	7.64x10 ⁻⁶
Any internalising and dyslipidemia	1.18 (1.06-1.31)	3.84x10 ⁻⁶
Any internalising and obesity	1.42 (1.26-1.61)	8.95x10 ⁻¹⁰
Any internalising T2D	1.56 (1.35-1.80)	7.06x10 ⁻¹⁰
Any internalising and CKD	1.37 (1.15-1.63)	4.15x10 ⁻⁶

Supplementary Table 8. Association of ICM-MM phenotypes with the presence of a ND-CNV excluding individuals with 16p11.2 proximal and distal deletions (N= 185).

	Male sex	Female sex	Difference
	OR (CI)	OR (CI)	p-value
Any internalising	1.20 (1.10-1.31)	1.25 (1.16-1.34)	0.512
Any cardiometabolic	1.09 (1.02-1.17)	1.25 (1.17-1.34)	0.004
Any ICM-MM	1.19 (1.08-1.32)	1.31 (1.20-1.43)	0.211
Any internalising and hypertension	1.12 (0.99-1.26)	1.31 (1.18-1.45)	0.063
Any internalising and dyslipidemia	1.19 (1.05-1.36)	1.34 (1.19-1.51)	0.214
Any internalising and obesity	1.39 (1.17-1.66)	1.55 (1.36-1.76)	0.328
Any internalising T2D	1.35 (1.13-1.61)	1.78 (1.51-2.10)	0.026
Any internalising and CKD	1.61 (1.30-1.99)	1.32 (1.08-1.62)	0.181

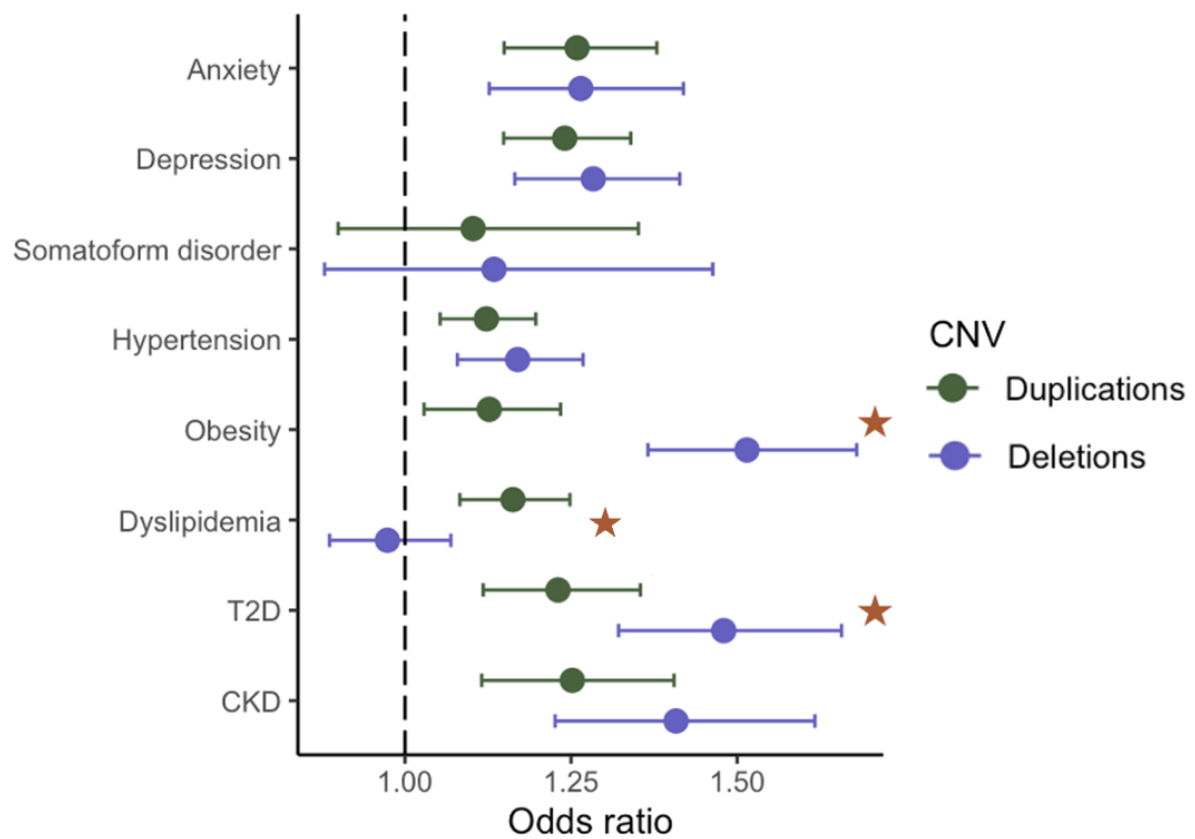
Supplementary Table 9. Association of ICM-MM phenotypes with ND-CNV for male and female sex.



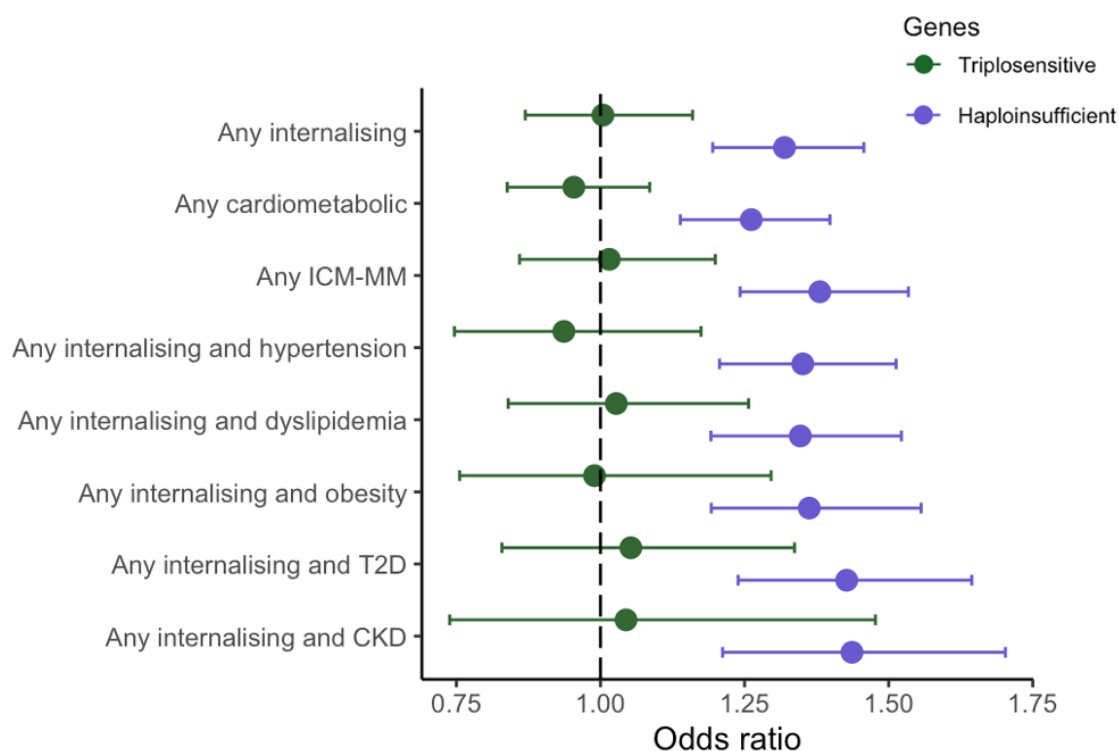
Supplementary Figure 3. Association of ND-CNVs with internalising and cardiometabolic conditions for male and female sex. Stars indicate a significant interaction of presence of ND-CNV and sex.

	Duplications	Deletions	Difference
	OR (CI)	OR (CI)	p-value
Any internalising	1.21 (1.13-1.29)	1.26 (1.16-1.38)	0.834
Any cardiometabolic	1.17 (1.10-1.24)	1.17 (1.08-1.26)	0.980
Any ICM-MM	1.21 (1.11-1.32)	1.32 (1.19-1.47)	0.430
Any internalising and hypertension	1.16 (1.05-1.28)	1.31 (1.17-1.48)	0.281
Any internalising and dyslipidemia	1.31 (1.18-1.47)	1.20 (1.04-1.38)	0.596
Any internalising and obesity	1.27 (1.10-1.46)	1.85 (1.59-2.15)	0.002
Any internalising T2D	1.45 (1.24-1.70)	1.72 (1.44-2.07)	0.267
Any internalising and CKD	1.34 (1.11-1.62)	1.61 (1.29-2.02)	0.439

Supplementary Table 10. Association of ICM-MM phenotypes with duplications and deletions.



Supplementary Figure 4. Association of duplications and deletions with internalising and cardiometabolic conditions. Stars indicate a suggested difference between deletions and duplications (p -value < 0.05).



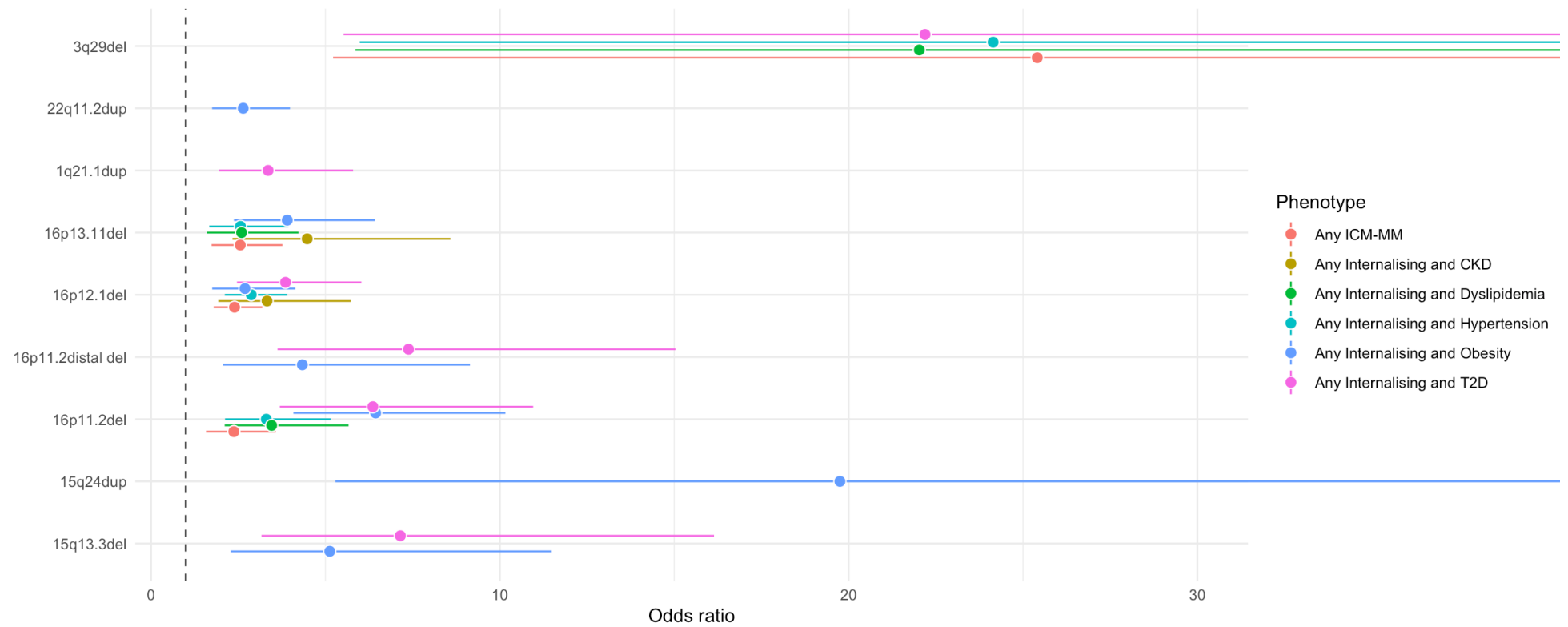
Supplementary Figure 5. Association of triplosensitive genes in duplications and haploinsufficient genes in deletions with ICM-MM. ORs represent an increase in risk by an increase of one gene

	Deletions		Duplications	
	Haploinsufficient genes	Total genes	Triplosensitive genes	Total genes
	OR (CI)	OR (CI)	OR (CI)	OR (CI)
Any internalising	1.31 (1.19-1.46) *	1.01 (1.00-1.01) *	1.01 (0.86-1.15)	1.01 (1.00-1.01) *
Any cardiometabolic	1.26 (1.14-1.40) *	1.01 (1.00-1.01) *	0.95 (0.84-1.08)	1.01 (1.00-1.01) *
Any ICM-MM	1.38 (1.24-1.53) *	1.01 (1.00-1.01) *	1.01 (0.86 -1.20)	1.01 (1.00-1.01) *
Any internalising and hypertension	1.35 (1.21-1.51) *	1 (1.00-1.01)	0.94 (0.75-1.17)	1.01 (1.00-1.01)
Any internalising and dyslipidemia	1.35 (1.19-1.52) *	1.01 (1.00-1.01) *	1.03 (0.84-1.25)	1.01 (1.00-1.01) *
Any internalising and obesity	1.36 (1.10-1.55) *	1.01 (1.01-1.03) *	0.99 (0.76-1.30)	1.01 (1.00-1.01) *
Any internalising and T2D	1.43 (1.24-1.64) *	1.01 (1.01-1.02) *	1.05 (0.83-1.34)	1.01 (1.00-1.01) *
Any internalising and CKD	1.44 (1.21-1.70) *	1.01 (1.00-1.01)	1.04 (0.74-1.48)	1.01 (1.00-1.01)

Supplementary Table 11. Association of haploinsufficient and total genes in deletions and triplosensitive and total genes in duplications with ICM-MM. ORs represent odds by an increase of one gene. Asterisks indicate statistical significance after multiple testing.

PRS	MDD		Anxiety		T2D		BMI		SBP		LDL		CKD	
	OR (CI)	p-value	OR (CI)	p-value	OR (CI)	p-value	OR (CI)	p-value	OR (CI)	p-value	OR (CI)	p-value	OR (CI)	p-value
Any ICM-MM	1.01 (0.94, 1.08)	0.857	1.03 (0.96,1.10)	0.438	1.00 (0.93,1.08)	0.983	0.98 (0.91,1.06)	0.668	0.96 (0.89,1.03)	0.269	1.03 (0.96,1.11)	0.351	1.02 (0.95,1.09)	0.606
Any internalising and hypertension	0.96 (0.8, 81.04)	0.323	1.01 (0.93,1.09)	0.842	1.02 (0.94,1.11)	0.616	1.01 (0.92,1.10)	0.902	0.98 (0.90,1.07)	0.678	1.06 (0.97,1.14)	0.183	1.01 (0.93,1.10)	0.775
Any internalising and dyslipidemia	1.04 (0.94, 1.14)	0.468	1.07 (0.97,1.17)	0.176	1.01 (0.92,1.12)	0.795	0.97 (0.87,1.07)	0.500	1.02 (0.93,1.12)	0.651	1.05 (0.95,1.15)	0.332	1.03 (0.94,1.13)	0.535
Any internalising and obesity	1.10 (0.98, 1.23)	0.094	1.15 (1.04,1.28)	0.010	0.97 (0.87,1.09)	0.642	0.98 (0.87,1.10)	0.738	1.02 (0.92,1.15)	0.667	1.02 (0.91,1.13)	0.748	1.07 (0.96,1.19)	0.237
Any internalising and T2D	0.93 (0.82, 1.07)	0.317	1.01 (0.89,1.14)	0.884	1.01 (0.88,1.16)	0.907	0.98 (0.85,1.13)	0.775	1.09 (0.96,1.25)	0.177	1.05 (0.93,1.20)	0.428	0.95 (0.84,1.08)	0.413
Any internalising and CKD	1.06 (0.90, 1.24)	0.486	1.18 (1.01,1.37)	0.037	0.88 (0.75,1.04)	0.143	0.94 (0.79,1.11)	0.470	1.05 (0.90,1.23)	0.549	1.18 (1.01,1.37)	0.039	1.01 (0.87,1.18)	0.893

Supplementary Table 12. Interaction of ND-CNVs and PRSs.



Supplementary Figure 6. Association of individual ND-CNVs and multimorbidity. Only significant associations after Bonferroni correction for multiple testing are included in the figure.

	Any internalising and hypertension			Any internalising and dyslipidemia			Any internalising and obesity			Any internalising and T2D			Any internalising and CKD			Any ICM-MM		
CNV	OR	CI	p-value	OR	CI	p-value	OR	CI	p-value	OR	CI	p-value	OR	CI	p-value	OR	CI	p-value
TAR del	1.22	0.59,2.54	0.593	1.07	0.43,2.66	0.881	0.35	0.05,2.51	0.295	1.09	0.27,4.46	0.9	2.15	0.68,6.87	0.195	0.97	0.48,1.96	0.941
TAR dup	1.1	0.79,1.51	0.574	1.3	0.91,1.84	0.145	1.55	1.03,2.34	0.037	1.8	1.14,2.86	0.012	1.27	0.68,2.38	0.457	1.39	1.08,1.8	0.012
1q21.1 del	0.83	0.41,1.71	0.617	0.74	0.3,1.83	0.52	1.71	0.8,3.68	0.168	1.13	0.36,3.55	0.839	1.04	0.26,4.24	0.954	0.92	0.52,1.65	0.786
1q21.1 dup	1.93	1.29,2.89	0.001	2.26	1.46,3.51	2.66E-04	1.51	0.8,2.86	0.206	3.36	1.94,5.79	1.40E-05	1.87	0.83,4.24	0.133	1.65	1.14,2.38	0.007
NRXN1 del	1.2	0.72,1.98	0.487	0.77	0.38,1.57	0.47	2.08	1.16,3.75	0.014	1.94	0.95,3.96	0.069	0.64	0.16,2.6	0.536	1.33	0.87,2.02	0.188
2q11.2 del	0.83	0.2,3.47	0.795	0.59	0.08,4.35	0.606	3.86	1.35,11.01	0.012	0	0,2,34E+43	0.875	0	0,4,83E+42	0.881	1.05	0.37,3	0.933
2q13 del	1.74	0.79,3.87	0.171	1	0.31,3.23	0.993	2.2	0.79,6.09	0.13	0	0,7,69E+32	0.839	1.19	0.16,8.7	0.861	1.27	0.6,2.7	0.539
2q13 dup	0.66	0.24,1.82	0.425	0.98	0.36,2.69	0.965	0.39	0.05,2.8	0.349	1.84	0.58,5.86	0.302	0.82	0.11,5.96	0.848	0.84	0.38,1.84	0.662
3q29 del	24.14	5.98,97.42	7.71E-06	22.03	5.86,82.82	4.73E-06	3.64	0.45,29.32	0.224	22.19	5.52,89.21	1.26E-05	19.24	3.88,95.44	2.96E-04	25.41	5.22,123.68	6.17E-05
WBS dup	0.79	0.1,5.99	0.817	2.4	0.54,10.66	0.251	1.86	0.24,14.13	0.549	2.41	0.31,18.66	0.399	4.41	0.57,34.04	0.155	1	0.22,4.48	1
8p23.1 dup	1.33	0.16,10.86	0.789	1.8	0.22,14.78	0.584	4.05	0.49,33.25	0.192	9.54	1.84,49.56	0.007	0	0,5,85E+32	0.872	4.49	1.07,18.9	0.041
15q11.2 del	0.97	0.82,1.15	0.737	0.94	0.77,1.16	0.557	1.23	0.97,1.56	0.08	1.05	0.78,1.43	0.734	1.24	0.9,1.71	0.182	1	0.87,1.16	0.952
15q11.2 dup	1.15	1,1.33	0.047	1.34	1.14,1.56	2.67E-04	1.22	1,1.5	0.054	1.36	1.07,1.71	0.01	1.21	0.91,1.61	0.2	1.15	1.02,1.3	0.024
PWS dup	0.81	0.11,6.11	0.837	1.22	0.16,9.22	0.848	0	0,4,69E+34	0.854	0	0,8,42E+34	0.866	0	0,1,378E+34	0.873	0.44	0.06,3.31	0.424
15q13.3 del	3.06	1.51,6.19	0.002	3.86	1.85,8.05	3.30E-04	5.12	2.28,11.49	7.35E-05	7.15	3.17,16.14	2.21E-06	1.26	0.17,9.17	0.823	2.16	1.11,4.21	0.023
15q24 dup	6.28	1.53,25.78	0.011	5.38	1.09,26.55	0.039	19.75	5.28,73.87	9.31E-06	6.33	0.79,50.99	0.083	8.28	0.98,70	0.052	6.17	1.63,23.37	0.007
16p13.11 del	2.56	1.67,3.94	1.75E-05	2.6	1.59,4.23	1.25E-04	3.9	2.38,6.42	7.68E-08	2.65	1.29,5.41	0.008	4.48	2.33,8.58	6.45E-06	2.56	1.74,3.77	2.06E-06
16p13.11 dup	1.18	0.94,1.47	0.157	1.32	1.03,1.7	0.029	1.18	0.84,1.65	0.336	1.71	1.22,2.41	0.002	1.63	1.09,2.43	0.016	1.09	0.89,1.33	0.392
16p12.1 del	2.87	2.11,3.9	1.63E-11	1.86	1.24,2.8	0.003	2.69	1.75,4.14	6.14E-06	3.85	2.46,6.03	3.54E-09	3.32	1.93,5.73	1.54E-05	2.39	1.8,3.19	2.66E-09
16p11.2 distal del	1.33	0.57,3.1	0.504	2.7	1.28,5.69	0.009	4.34	2.06,9.15	1.16E-04	7.38	3.63,15.03	3.58E-08	2.39	0.58,9.86	0.227	1.81	0.95,3.42	0.069
16p11.2 distal dup	2.06	1.29,3.29	0.002	1.92	1.1,3.34	0.022	0.8	0.29,2.16	0.654	0.64	0.16,2.57	0.527	1.35	0.43,4.27	0.605	1.77	1.16,2.71	0.008
16p11.2 del	3.3	2.12,5.15	1.24E-07	3.46	2.11,5.66	8.42E-07	6.44	4.08,10.16	1.20E-15	6.36	3.69,10.96	2.63E-11	3.21	1.3,7.93	0.011	2.37	1.58,3.57	3.46E-05
16p11.2 dup	0.76	0.38,1.49	0.417	0.84	0.39,1.81	0.665	0.61	0.19,1.91	0.396	1.25	0.46,3.37	0.665	2.09	0.85,5.13	0.108	1.04	0.63,1.71	0.89
17p13.3 YWHA del	0.98	0.23,4.16	0.979	0.69	0.09,5.13	0.72	4.96	1.71,14.45	0.003	3.69	0.87,15.65	0.076	2.7	0.36,20.11	0.333	1.41	0.48,4.1	0.533
17p13.3 YWHA Edup	3.68	0.73,18.59	0.115	2.25	0.27,18.56	0.452	4.7	0.57,38.44	0.149	5.73	0.7,47.05	0.104	7.64	0.9,64.72	0.062	1.16	0.14,9.84	0.892
Potocki Lupski	2.25	0.26,19.47	0.461	0	0,0	0.818	0	0,1,54E+38	0.88	0	0,2,59E+38	0.888	0	0,1,47E+38	0.893	1.47	0.17,12.77	0.727
17q11.2 del NF1	0	0,0	0.75	0	0,2,97E+28	0.833	3.34	0.42,26.52	0.255	0	0,1,01E+29	0.854	0	0,6,32E+48	0.901	0.88	0.11,6.98	0.902
17q12 del	3.85	0.79,18.74	0.095	5.46	1.12,26.71	0.036	0	0,4,04E+30	0.857	12.9	2.64,63.12	0.002	10.28	1.25,84.54	0.03	2.11	0.43,10.23	0.355
17q12 dup	1.49	0.81,2.73	0.196	0.82	0.33,2.02	0.665	1.84	0.8,4.2	0.149	1.21	0.38,3.82	0.747	2.99	1.21,7.41	0.018	1.3	0.75,2.26	0.352
22q11.2 del	3.74	0.79,17.73	0.097	0	0,5,75E+28	0.843	3.22	0.41,25.62	0.269	0	0,1,47E+29	0.861	0	0,2,05E+49	0.91	1.79	0.37,8.6	0.468
22q11.2 dup	1.26	0.85,1.87	0.244	1.5	0.98,2.3	0.063	2.64	1.75,3.98	3.70E-06	1.75	0.96,3.2	0.069	0.87	0.32,2.35	0.79	1.23	0.88,1.71	0.22
22q11.2 distal del	0	0,0	0.829	0	0,3,76E+24	0.839	0	0,5,47E+24	0.846	0	0,2,86E+42	0.901	0	0,8,65E+41	0.907	0	0,5,80E+23	0.808
22q11.2 distal dup	1.77	0.39,7.93	0.458	1.19	0.15,9.12	0.868	0	0,8,99E+23	0.821	0	0,1,95E+41	0.881	0	0,1,04E+41	0.884	1.08	0.24,4.9	0.923
																		0.593

Supplementary Table 13. Association of each of the ND-CNVs with ICM-MM.

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