Supplementary material

McGrath JJ, Lim CCW, Plana-Ripoll O, Holtz Y, Agerbo A, Momen NC, Mortensen PB, Pedersen CB, Abdulmalik J, Aguilar-Gaxiola S, Al-Hamzawi A, Alonso J, Bromet EJ, Bruffaerts R, Bunting B, Caldas de Almeida JM, de Girolamo G, De Vries YA, Florescu S, Gureje O, Haro JM, Harris MH, Hu C, Karam EG, Kawakami N, Kiejna A, Kovess-Masfety V, Lee S, Mneimneh Z, Navarro-Mateu F, Orozco R, Posada-Villa J, Roest AM, Saha S, Scott KM, Stagnaro JC, Stein DJ, Torres Y, Viana MC, Ziv Y, Kessler RC, de Jonge P.

Comorbidity within mental disorders: a comprehensive analysis based on 145,990 survey respondents from 27 countries.

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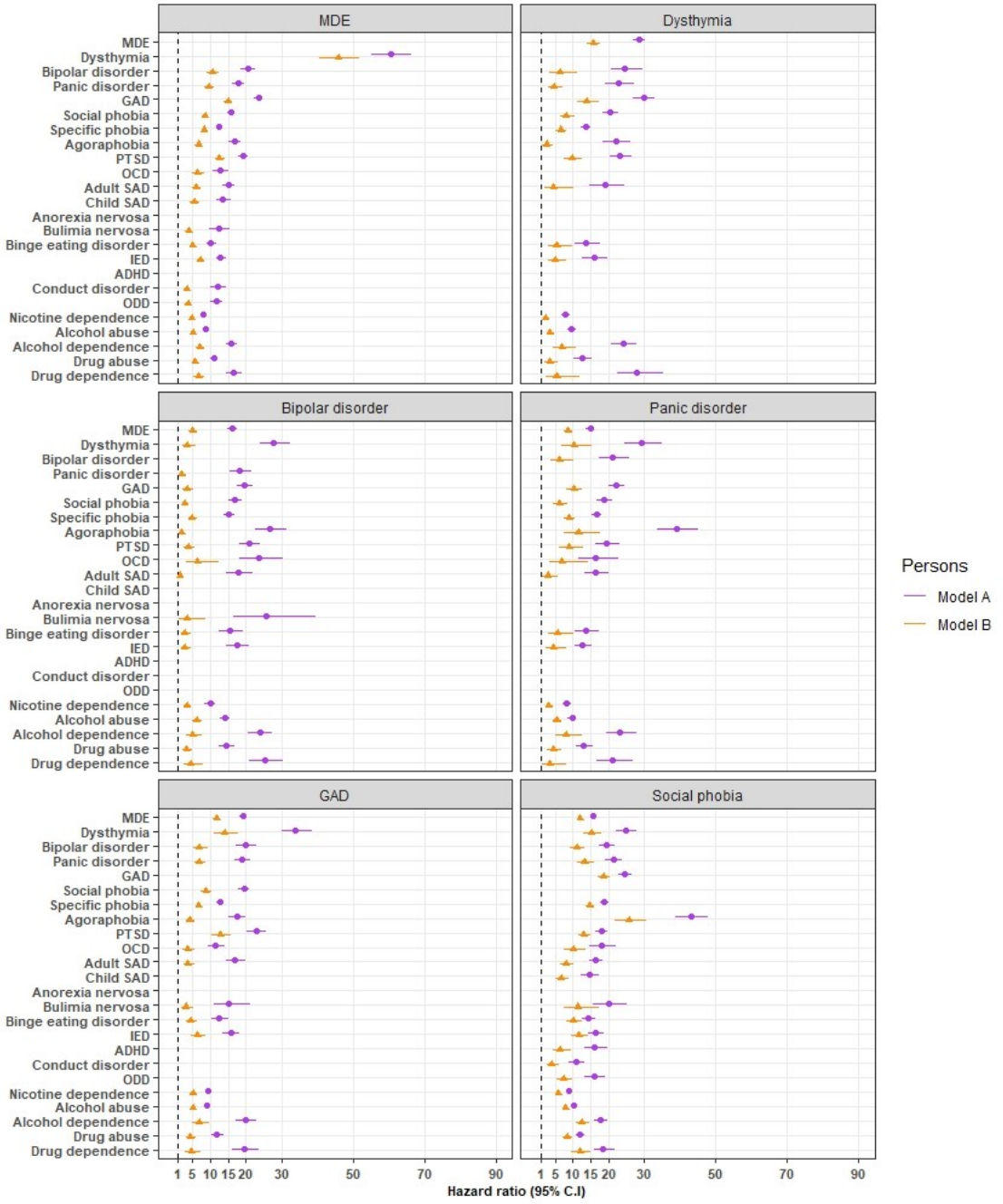
Supplementary Figure 1. Pairwise associations

Risks of developing a subsequent later disorder among persons with versus those without a prior disorder

Each panel shows the pairwise association between prior disorders and later disorders. Estimates were obtained via Cox proportional hazards regression model adjusting for age-cohort, sex, and country (Model A – purple circles in the plot), with further adjustment for type and number of mental disorders with onset preceding the prior disorder (Model B –orange triangles in the plot). Results were displayed in the form of Hazard ratios (HRs) and 95% confidence intervals (CIs). A vertical line at x = 1 representing "null effect" is also plotted in each panel. If the confidence intervals for the estimates overlap with this line, we have no evidence against the null hypothesis that the risk of developing a subsequent later disorder are the same among persons with prior disorder compared to those without. Estimates were not shown for disorder pairs with less than 30 cases due to unstable estimates. Abbreviations: Major Depressive Episode – MDE; Generalized Anxiety Disorder – GAD; Attention Deficit Hyperactivity Disorder (ADHD); Obsessive Compulsive Disorder (OCD); Post-Traumatic Stress Disorder (PTSD); Separation Anxiety Disorder (SAD); Intermittent Explosive Disorder (IED); Oppositional Defiant Disorder (ODD).


MDE
Dysthymia
Bipolar disorder
Panic disorder
GAD
Social phobia
Specific phobia
Agoraphobia
PTSD
OCD
Adult SAD
Child SAD
Anorexia nervosa
Bulimia nervosa
Binge eating disorder
IED
ADHD
Conduct disorder
ODD
Nicotine dependence
Alcohol abuse
Alcohol dependence
Drug abuse
Drug dependence
1 5 10 15 20 30 50 70 90
Hazard ratio (95% C.I)
Persons
Model A
Model B

Specific phobia
Agoraphobia
PTSD
Adult SAD
Child SAD
Anorexia nervosa
MDE
Dysthymia
Bipolar disorder
Panic disorder
GAD
Social phobia
Specific phobia
Agoraphobia
PTSD
OCD
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Drug abuse
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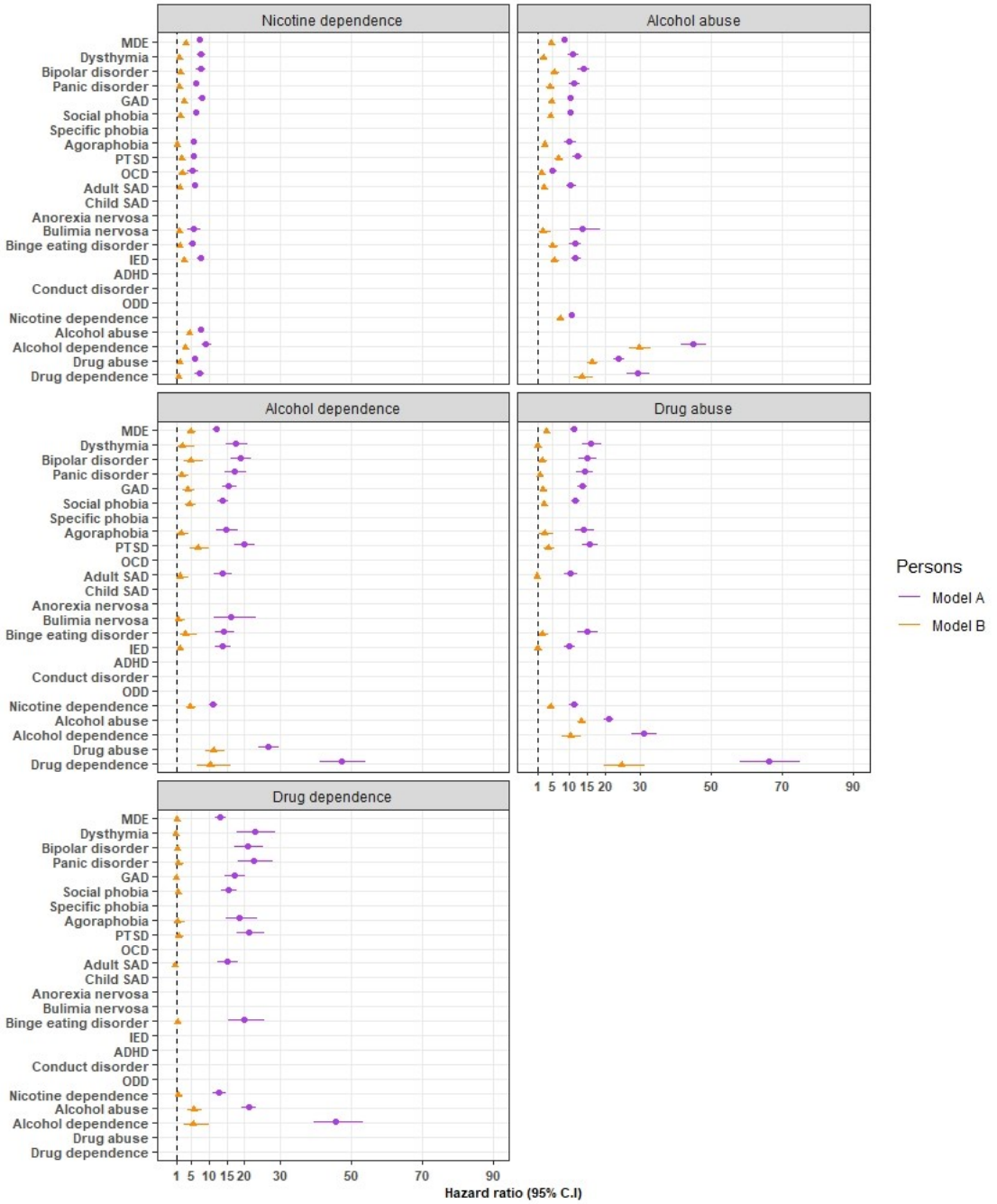
1 5 10 15 20 30 50 70 90
Hazard ratio (95% C.I)
Persons
Model A
Model B


Nicotine dependence
Alcohol abuse
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Drug abuse
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MDE
Dysthymia
Bipolar disorder
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Nicotine dependence
Alcohol abuse
Alcohol dependence
Drug abuse
Drug dependence
1 5 10 15 20 30 50 70 90
Hazard ratio (95% C.I)
Persons
Model A
Model B

Supplementary Figure 2. Sex-specific pairwise associations

Risks of developing a subsequent later disorder among persons with versus those without a prior disorder, by sex

The following figures show pairwise hazard ratios, estimated separately for men (blue triangles in the plot) and women (pink circles in the plot). The prior disorders are listed at the top of each panel and later disorders listed on the Y-axis. Estimates were obtained via Cox proportional hazards regression model adjusting for age-cohort, sex, and country with further adjustment for type and number of mental disorders with onset preceding the prior disorder (Model B). A vertical line at x = 1 representing "null effect" is also plotted in each panel. Estimates were not shown for disorder pairs with less than 30 cases due to unstable estimates. Abbreviations: Major Depressive Episode – MDE; Generalized Anxiety Disorder – GAD; Attention Deficit Hyperactivity Disorder (ADHD); Obsessive Compulsive Disorder (OCD); Post-Traumatic Stress Disorder (PTSD); Separation Anxiety Disorder (SAD); Intermittent Explosive Disorder (IED); Oppositional Defiant Disorder (ODD).

MDE
Dysthymia
Bipolar disorder
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Specific phobia
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Child SAD
Anorexia nervosa
Bulimia nervosa
Binge eating disorder
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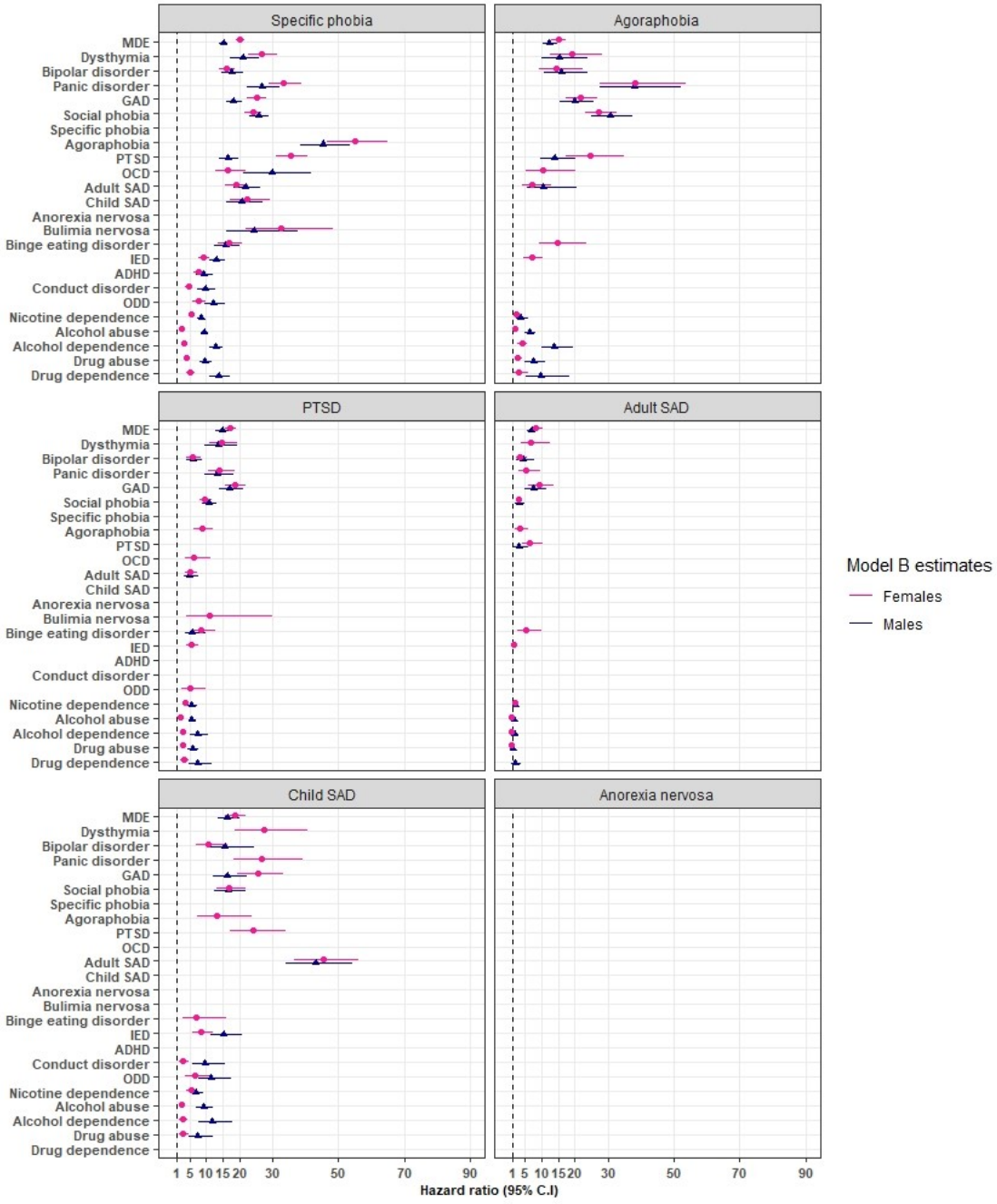
ADHD
Conduct disorder
ODD
Nicotine dependence
Alcohol abuse
Alcohol dependence
Drug abuse
Drug dependence
1 5 10 15 20 30 50 70 90
Hazard ratio (95% C.I)
Model B estimates
Females
Males


Specific phobia
Agoraphobia
PTSD
Adult SAD
Child SAD
Anorexia nervosa
MDE
Dysthymia
Bipolar disorder
Panic disorder
GAD
Social phobia
Specific phobia
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PTSD
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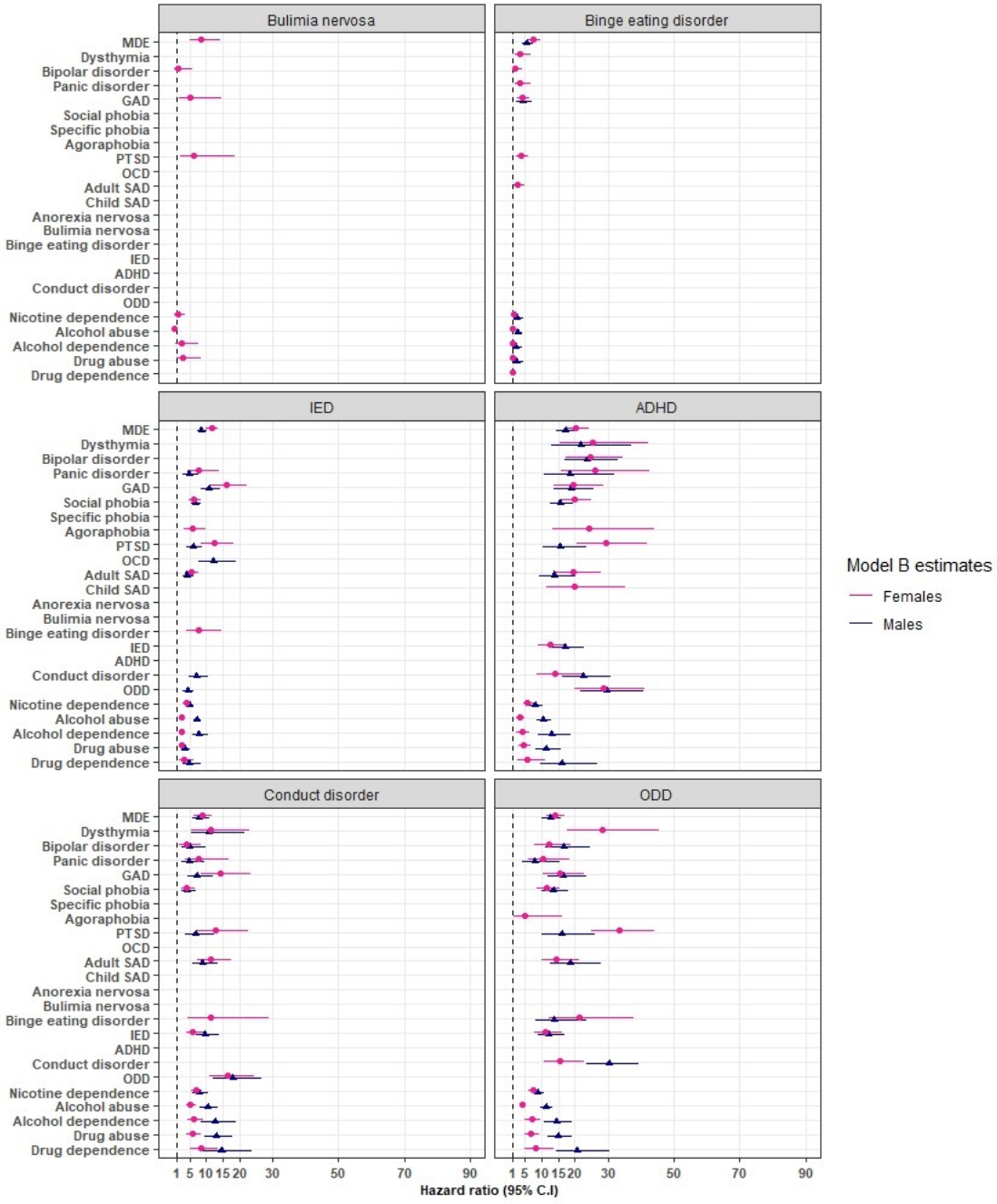
Nicotine dependence
Alcohol abuse
Alcohol dependence
Drug abuse
Drug dependence
1 5 10 15 20 30 50 70 90
Hazard ratio (95% C.I)
Model B estimates
Females
Males


Bulimia nervosa
Binge eating disorder
IED
ADHD
Conduct disorder
ODD
MDE
Dysthymia
Bipolar disorder
Panic disorder
GAD
Social phobia
Specific phobia
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1 5 10 15 20 30 50 70 90
Hazard ratio (95% C.I)
Model B estimates
Females
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Nicotine dependence
Alcohol abuse
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Drug abuse
Drug dependence
1 5 10 15 20 30 50 70 90
Hazard ratio (95% C.I)
Model B estimates
Females
Males

Supplementary Figure 3. Lagged associations

Lagged associations between prior disorders and subsequent later disorders

Each panel shows the risk of developing a subsequent later disorder conditioned on the time since onset of prior disorder. Estimates were obtained via Cox proportional hazards regression model adjusting for age-cohort, sex, and country (Model A – purple circles), with further adjustment for type and number of mental disorders with onset preceding the prior disorder (Model B – orange triangles). Results were displayed in the form of Hazard ratios (HRs) [shown in a log scale] and 95% confidence intervals (CIs). A horizontal line at y = 1 representing "null effect" is also plotted in each panel. The reference category is those without the specific prior disorder. Estimates with less than 30 cases were not shown. Later disorders are listed at the top of each panel. Abbreviations: Major Depressive Episode – MDE; Generalized Anxiety Disorder – GAD; Attention Deficit Hyperactivity Disorder (ADHD); Obsessive Compulsive Disorder (OCD); Post-Traumatic Stress Disorder (PTSD); Separation Anxiety Disorder (SAD); Intermittent Explosive Disorder (IED); Oppositional Defiant Disorder (ODD).

Figure 3a. Risk of later disorders in those with versus those without major depressive episode (MDE)

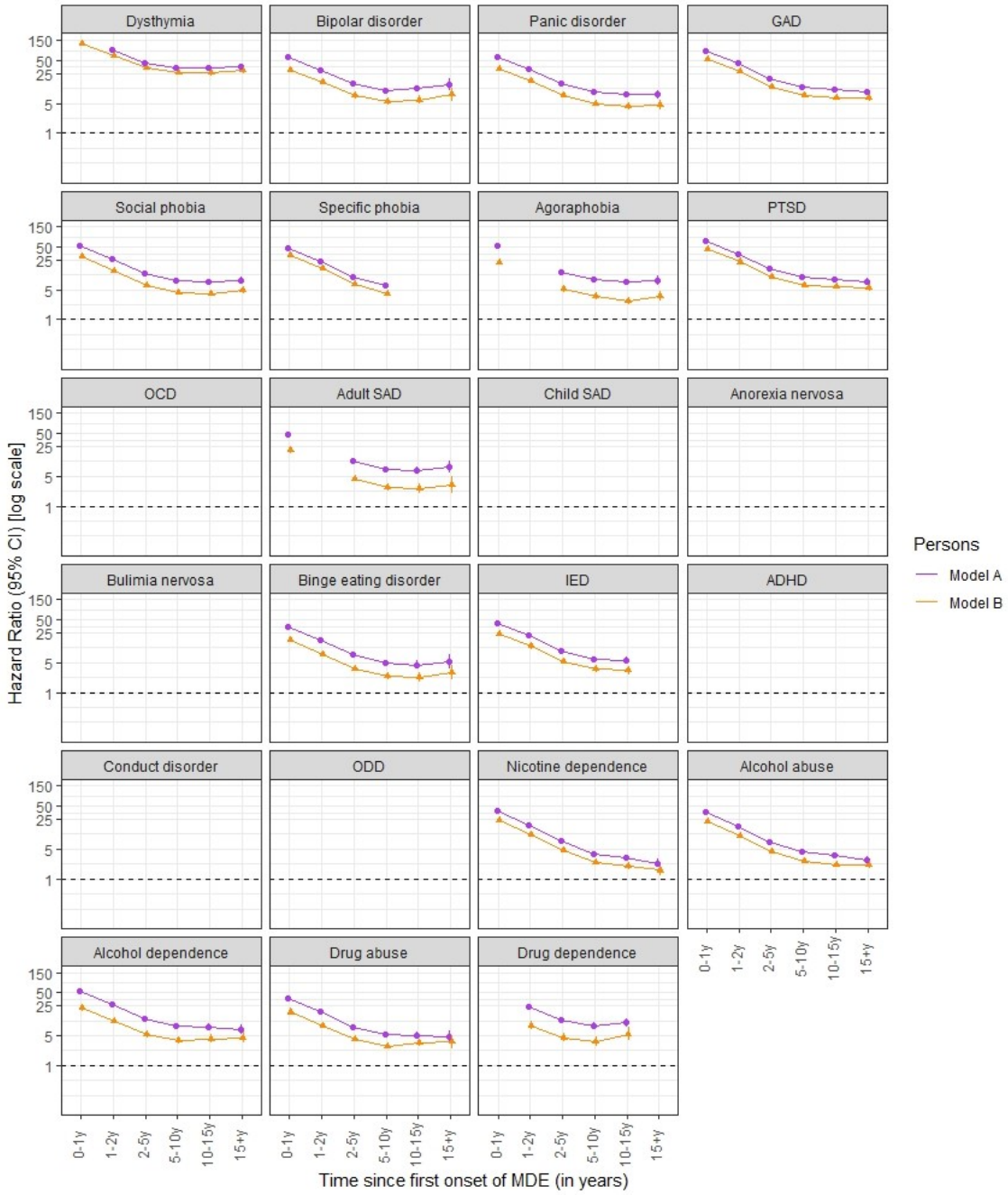


Figure 3b. Risk of later disorders in those with versus those without dysthymia

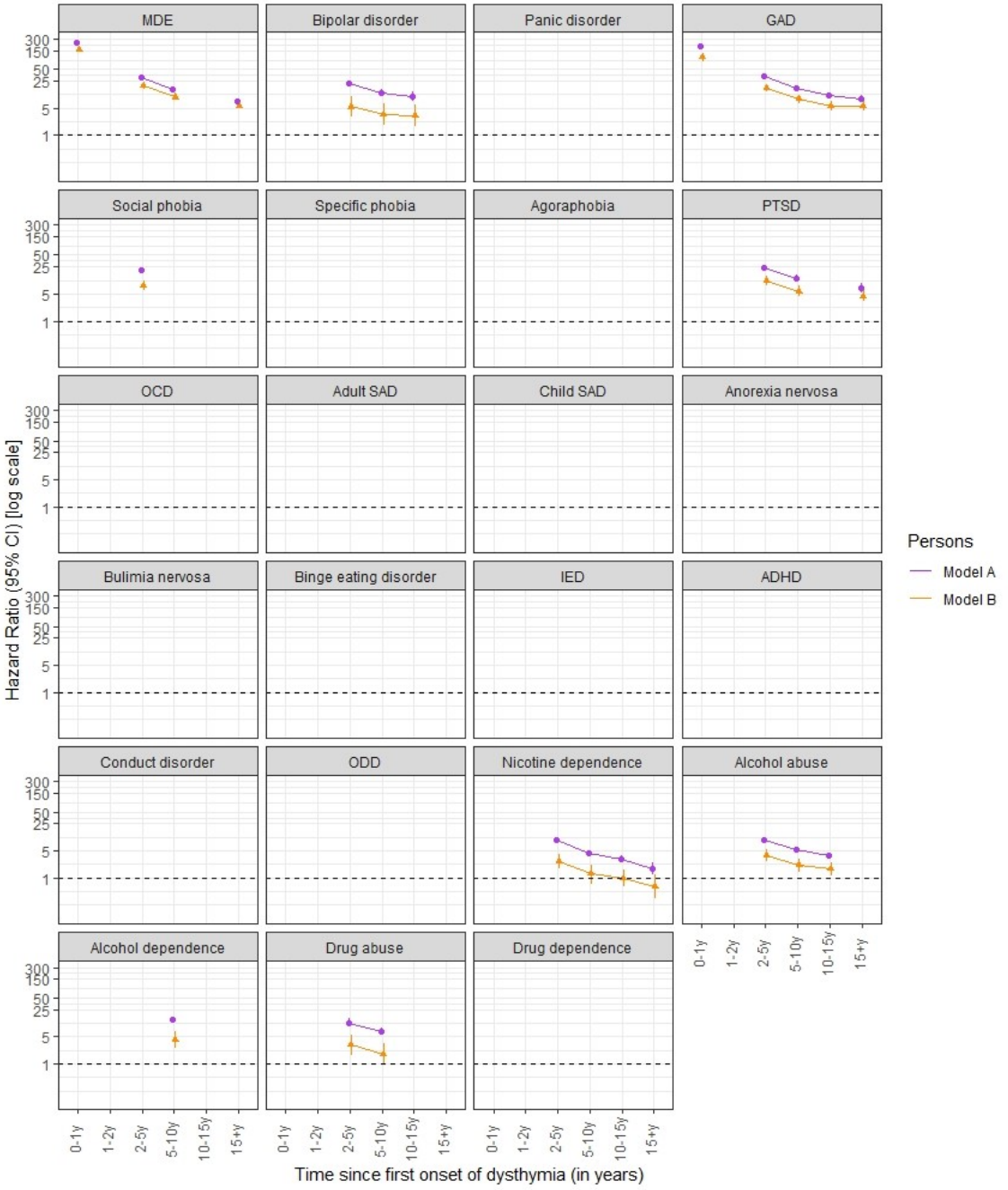


Figure 3c. Risk of later disorders in those with versus those without bipolar disorder

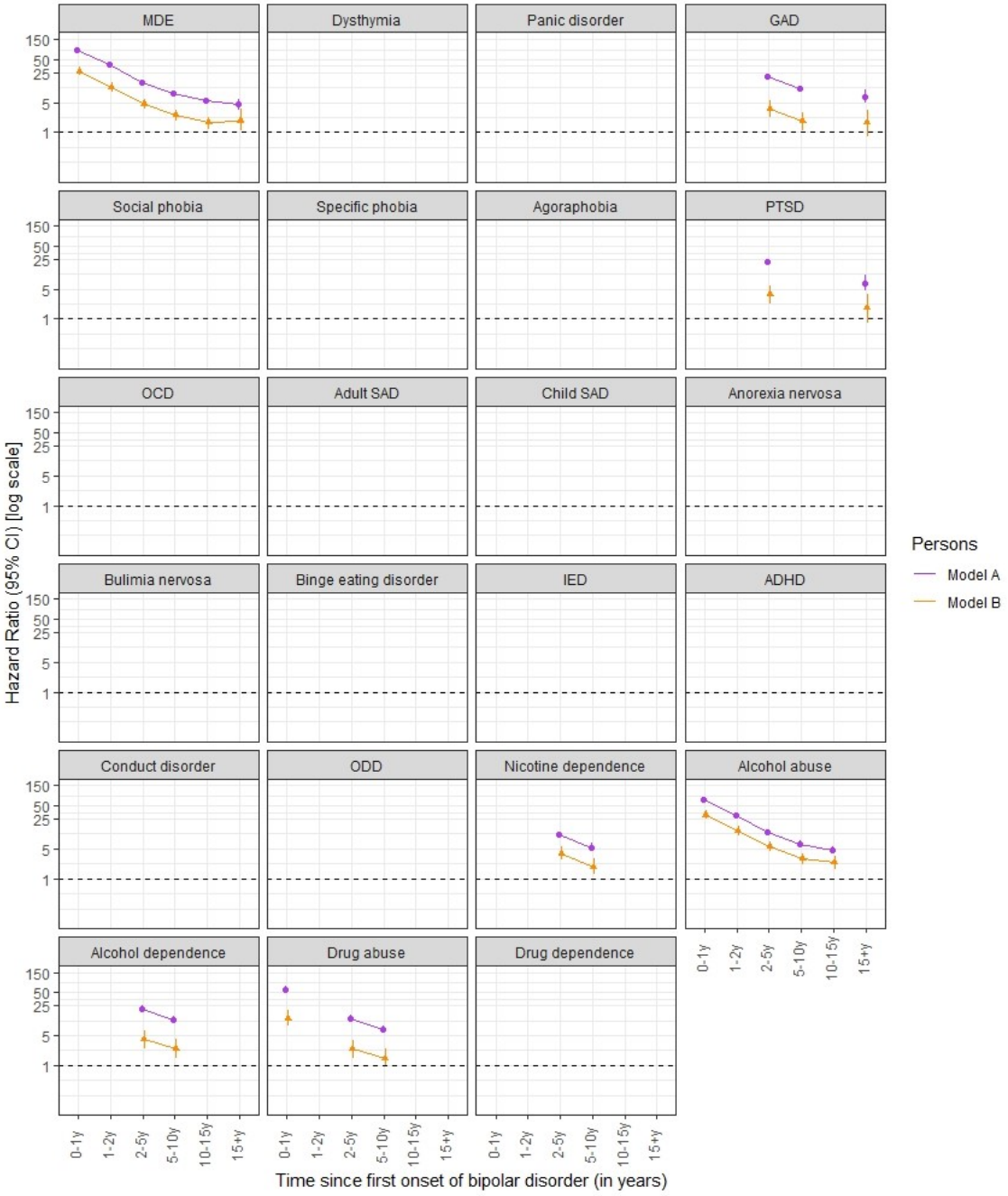


Figure 3d. Risk of later disorders in those with versus those without panic disorder

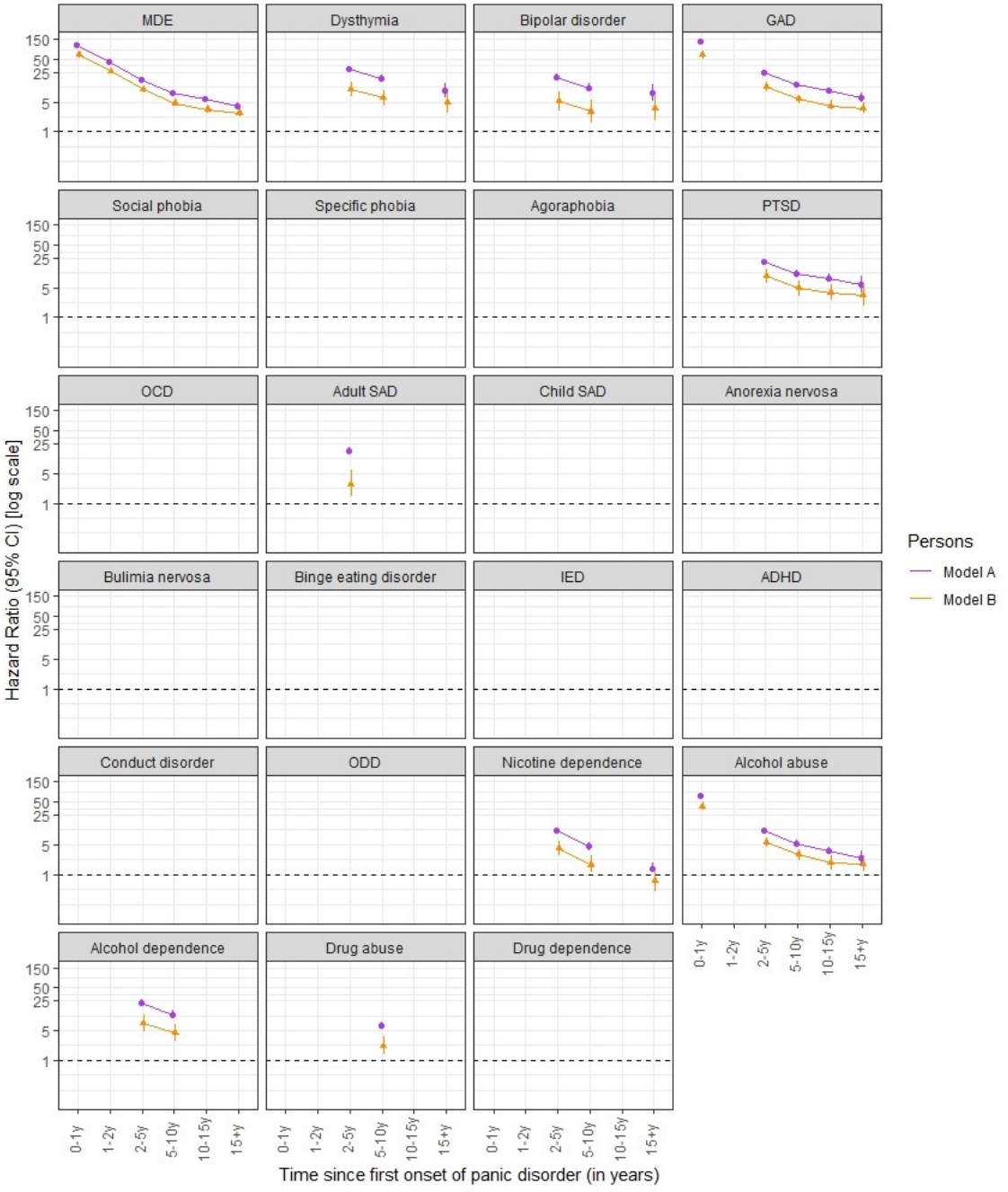


Figure 3e. Risk of later disorders in those with versus those without generalized anxiety disorder (GAD)

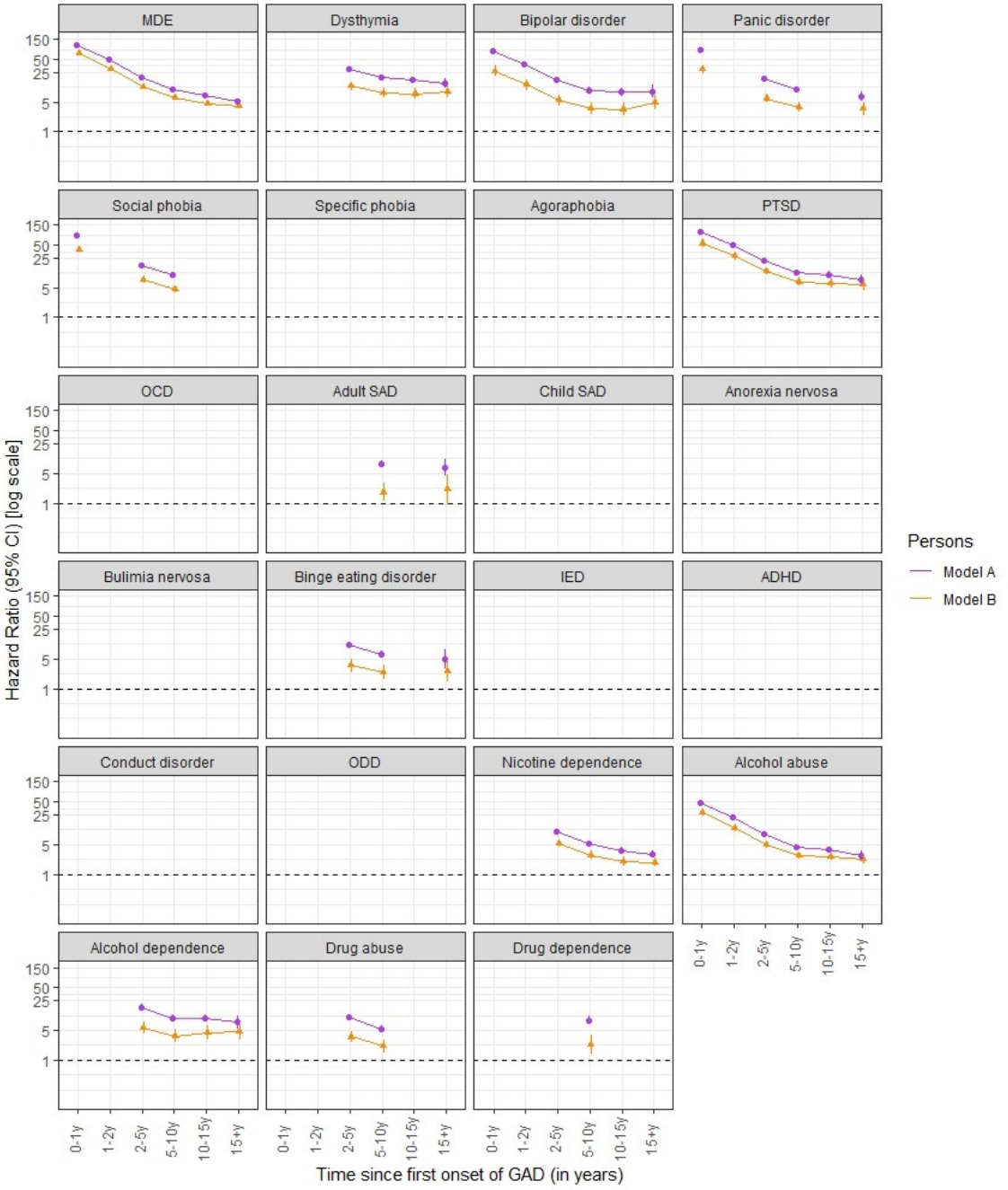


Figure 3f. Risk of later disorders in those with versus those without social phobia

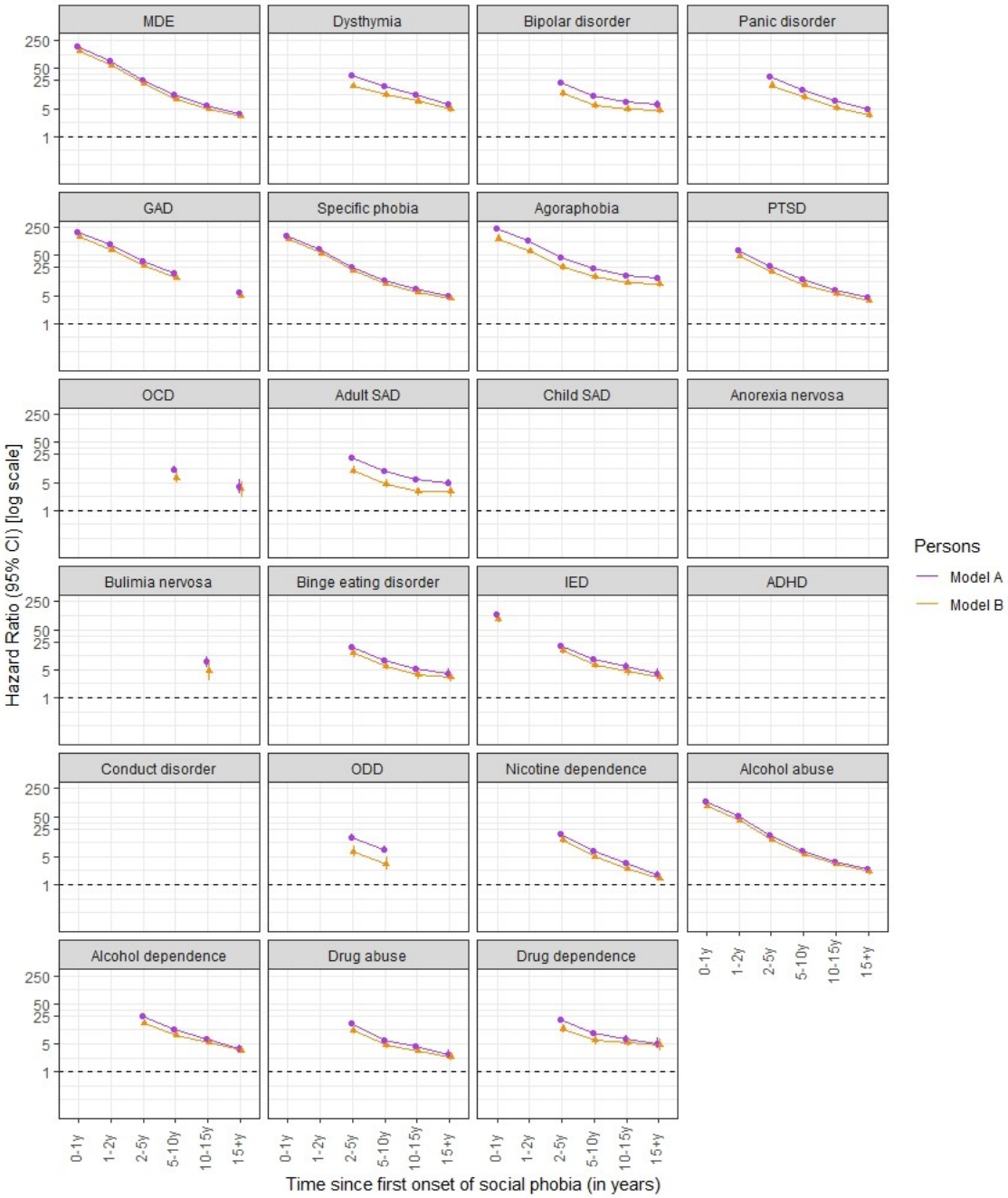


Figure 3g. Risk of later disorders in those with versus those without specific phobia

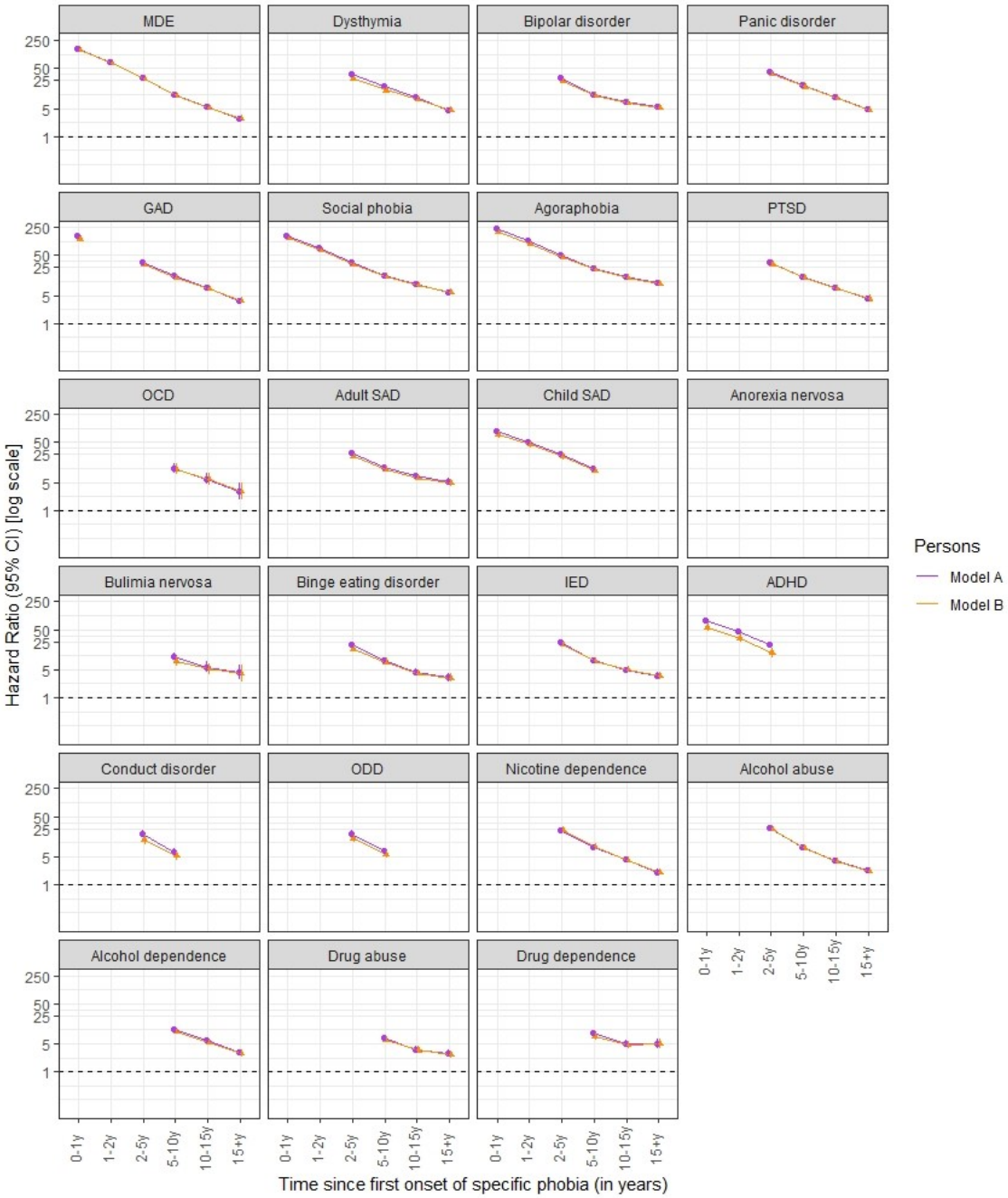


Figure 3h. Risk of later disorders in those with versus those without agoraphobia

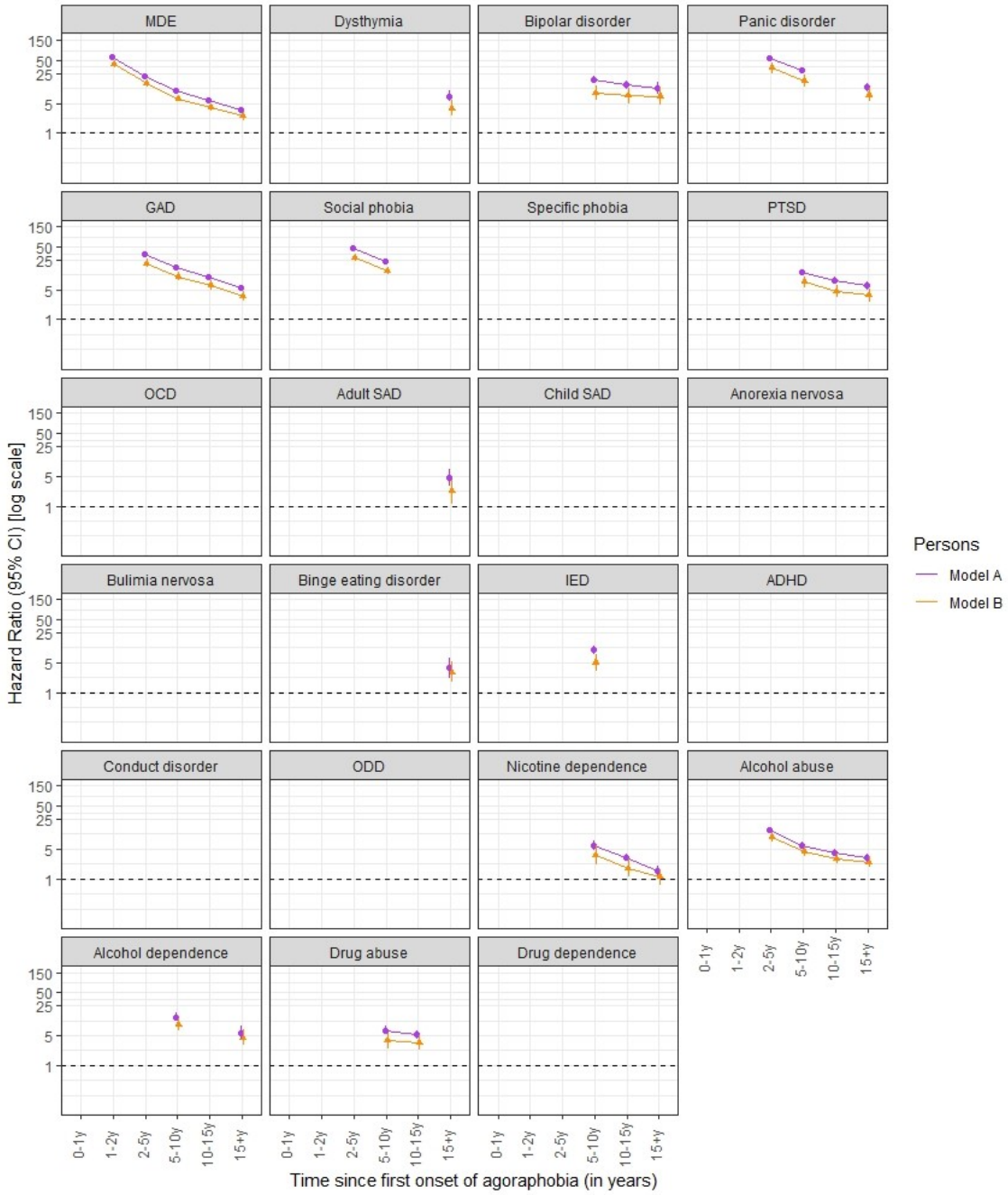


Figure 3i. Risk of later disorders in those with versus those without post-traumatic stress disorder (PTSD)

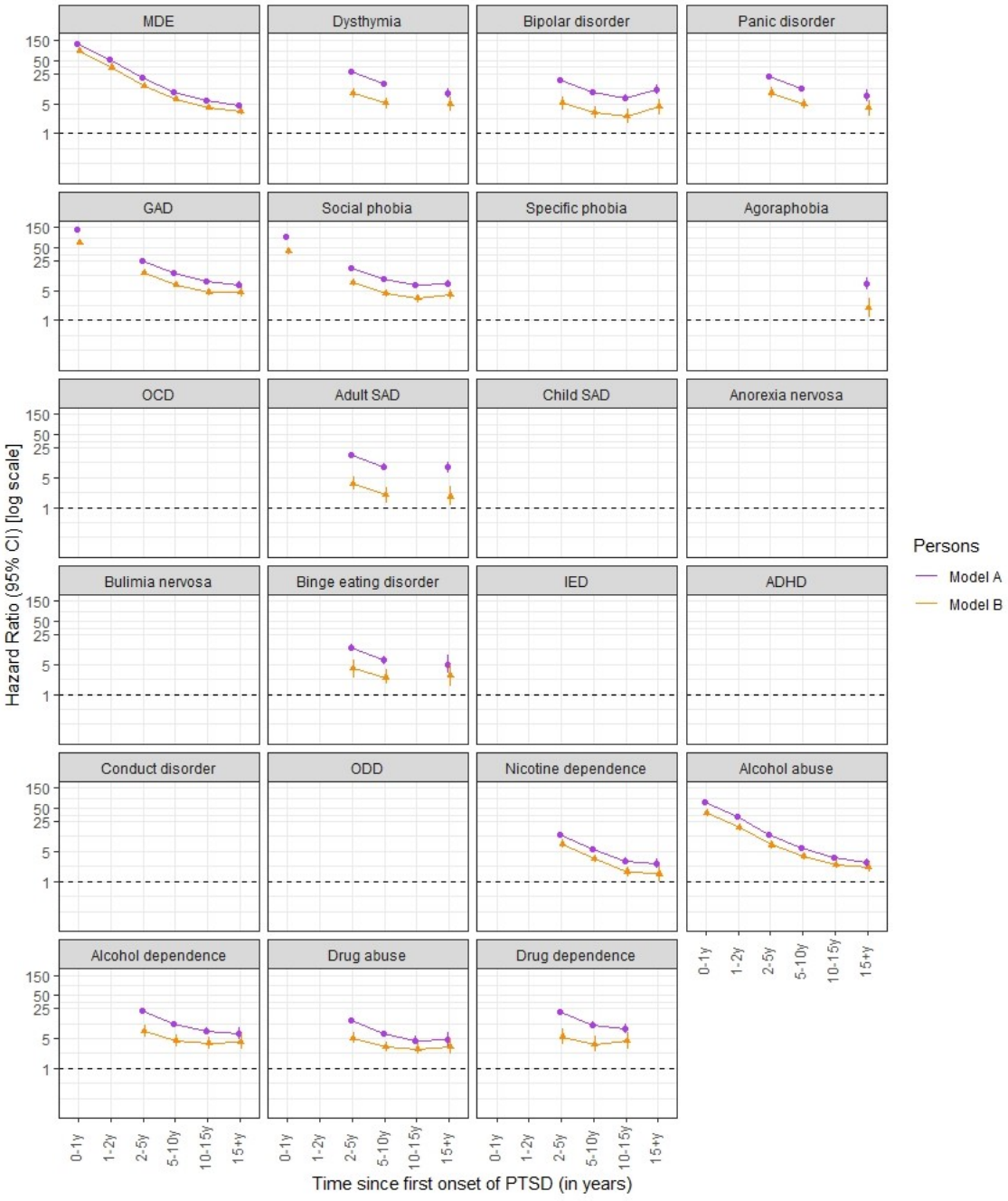


Figure 3j. Risk of later disorders in those with versus those obsessive compulsive disorder (OCD)

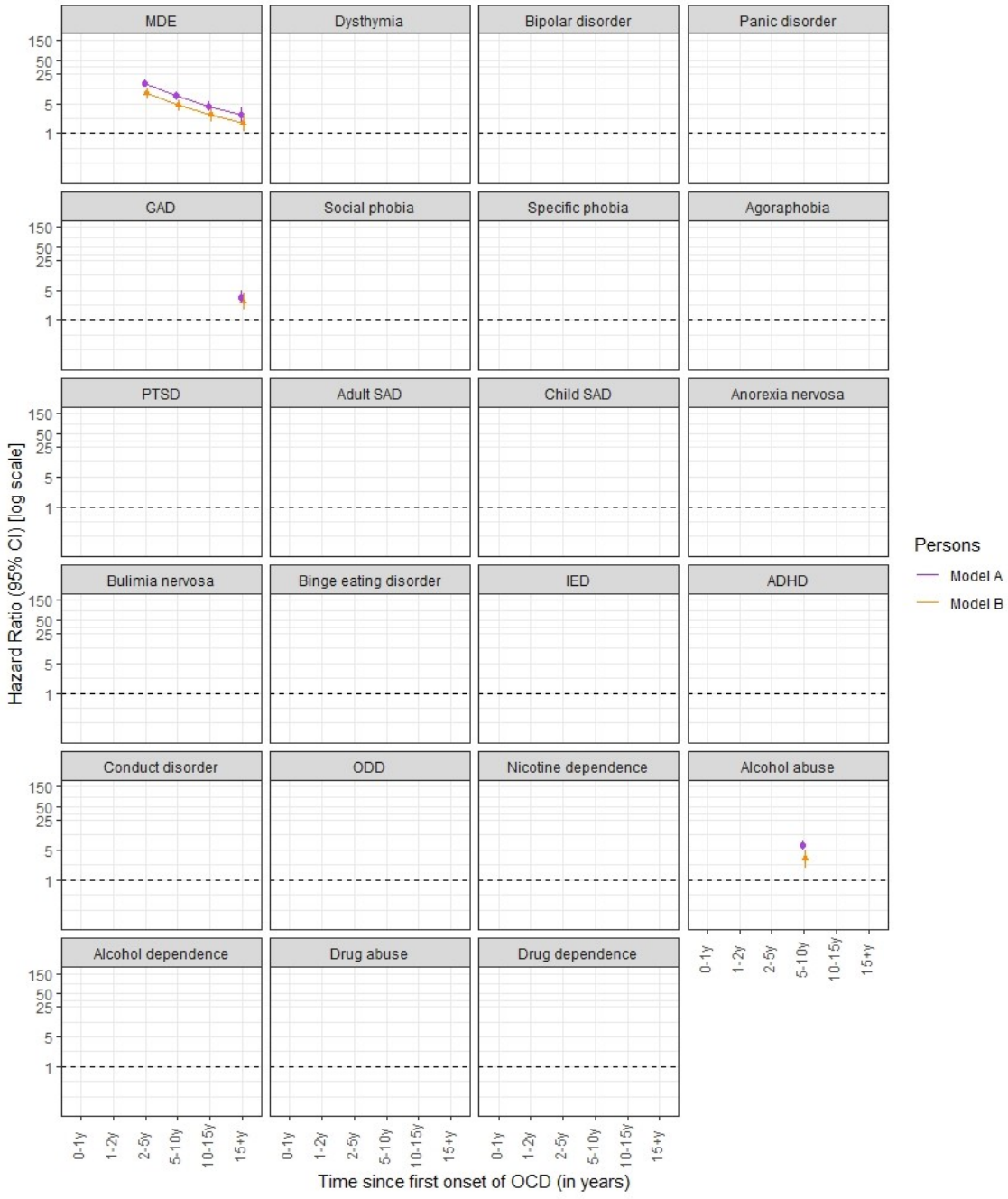


Figure 3k. Risk of later disorders in those with versus those without adult separation anxiety disorder

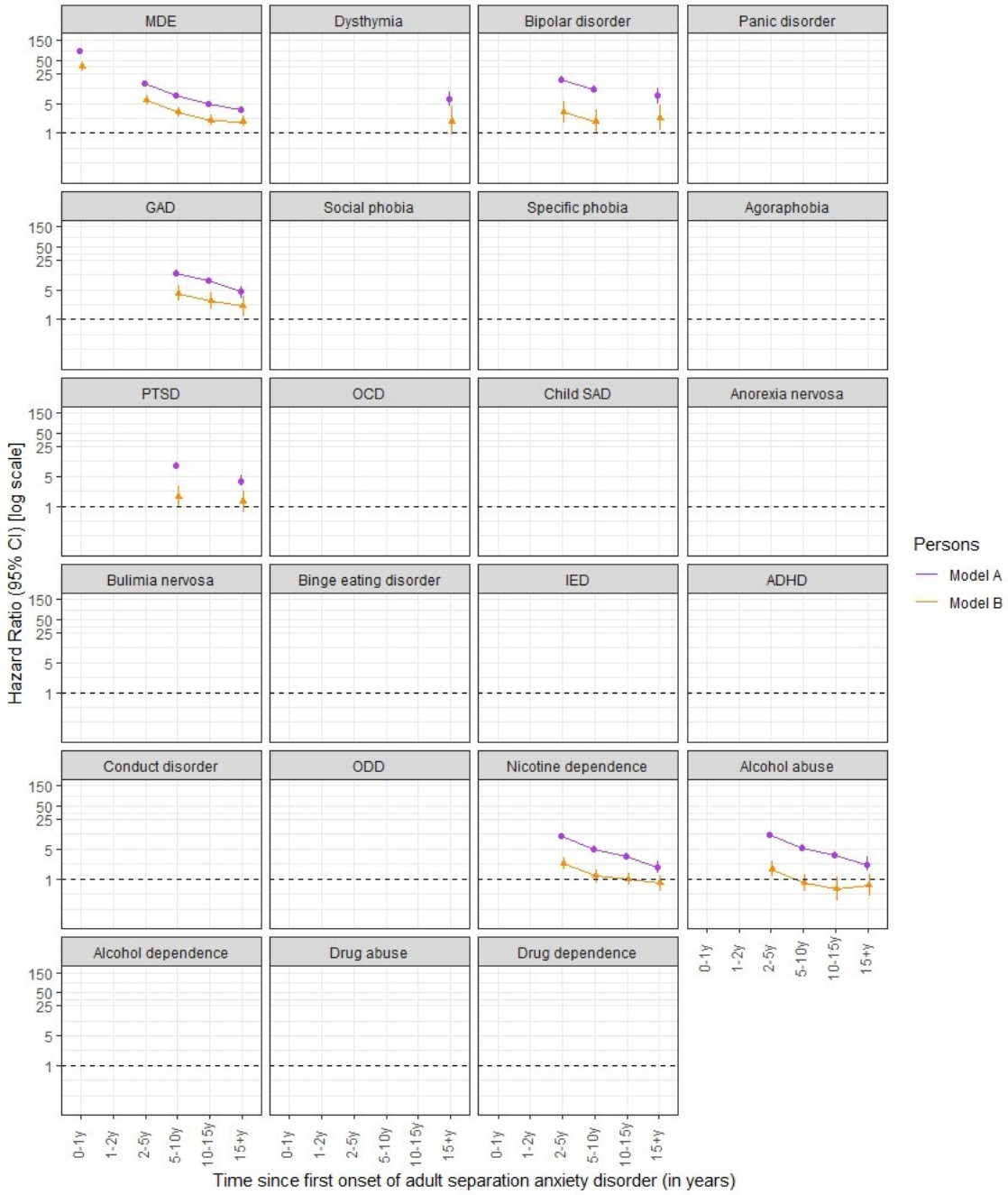


Figure 3l. Risk of later disorders in those with versus those without child separation anxiety disorder

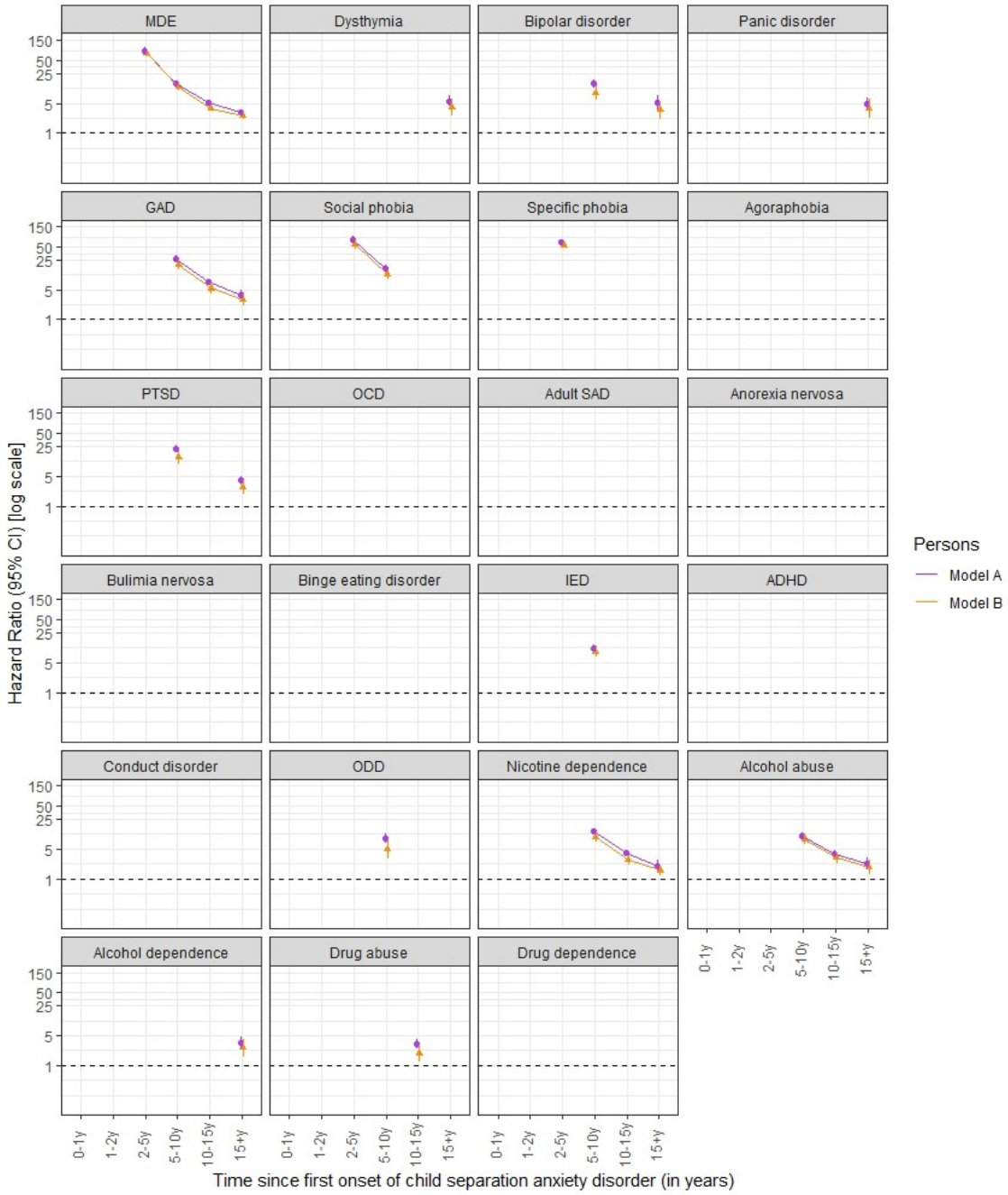


Figure 3m. Risk of later disorders in those with versus those without anorexia nervosa

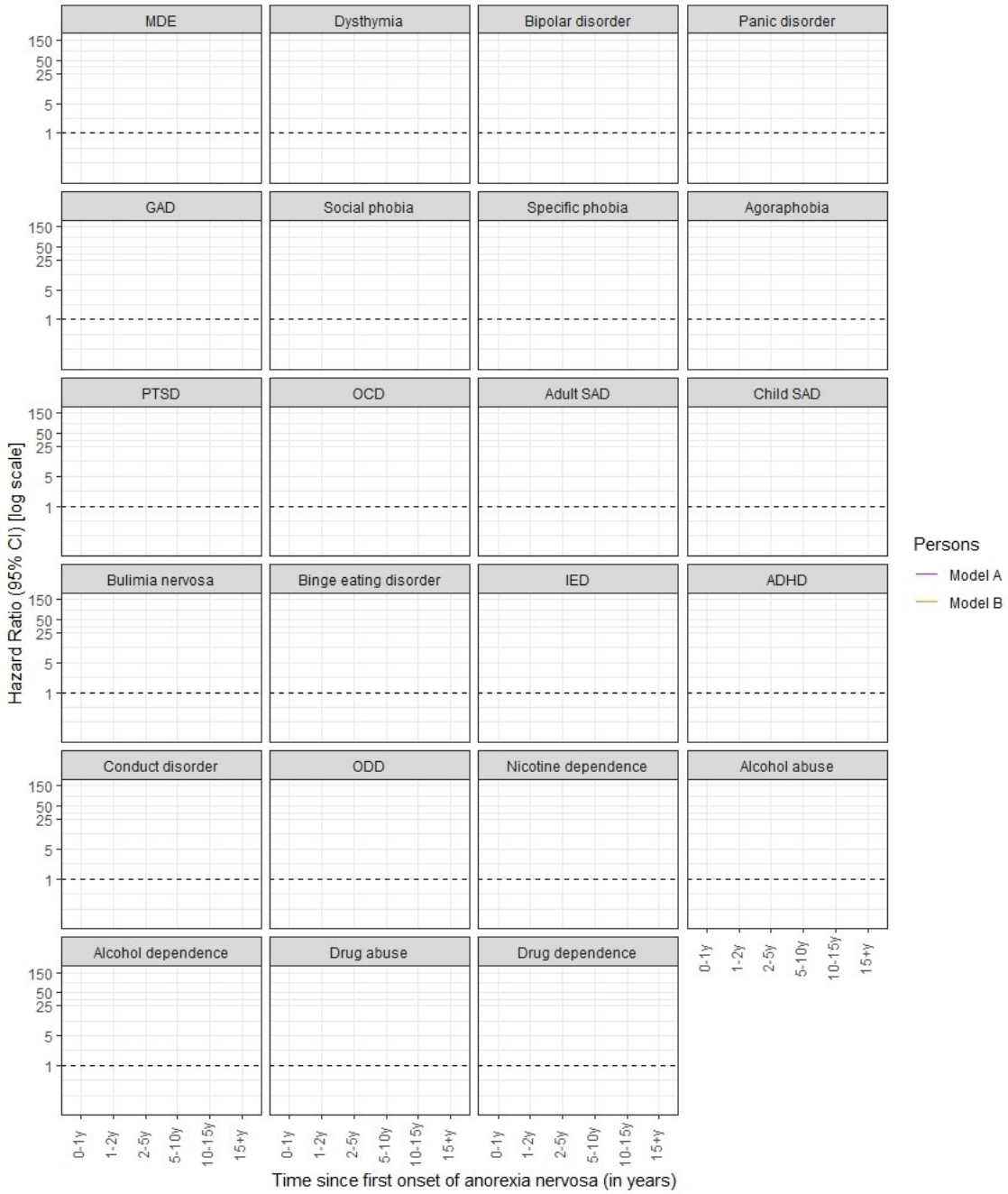


Figure 3n. Risk of later disorders in those with versus those without bulimia nervosa

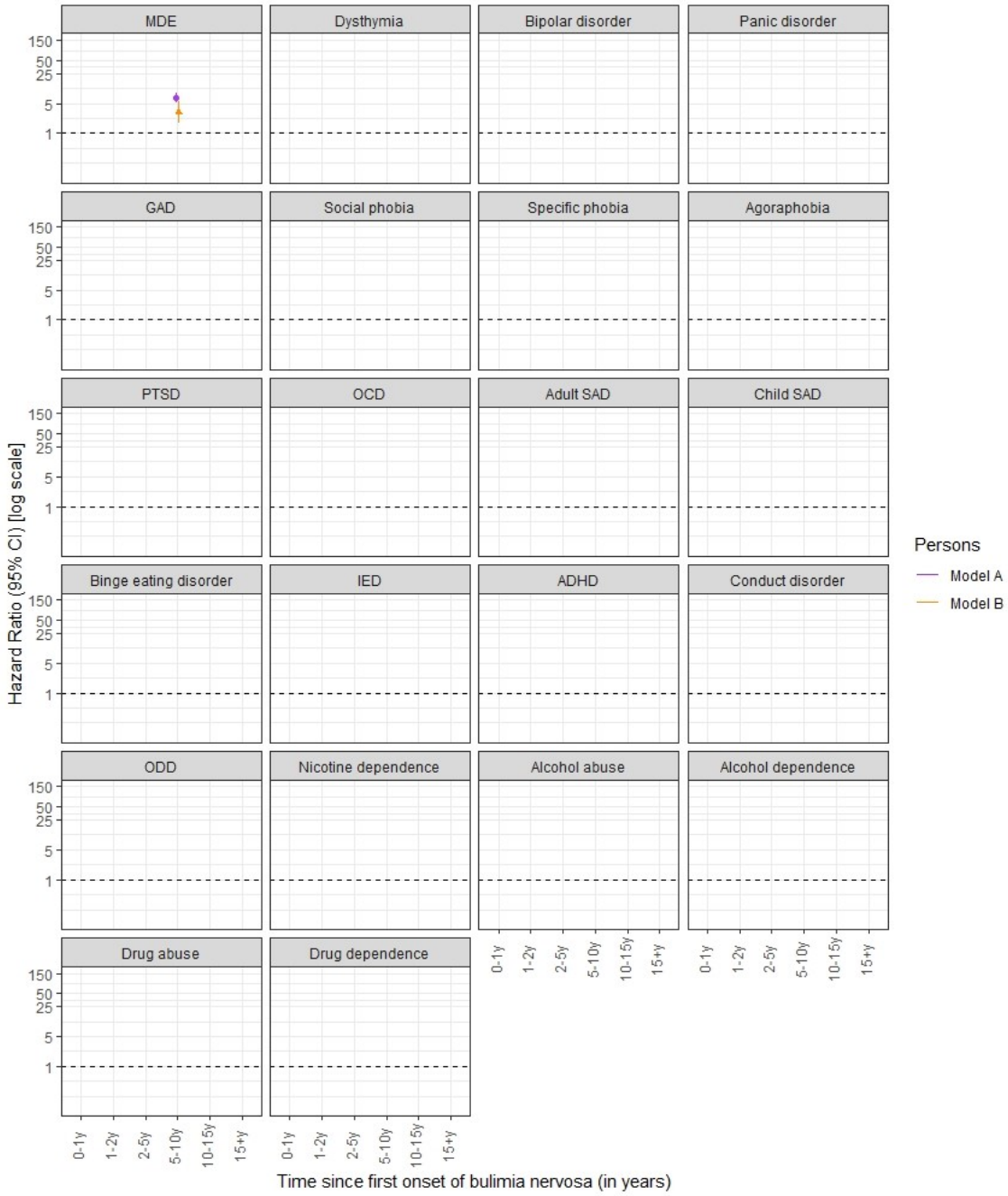


Figure 3o. Risk of later disorders in those with versus those without binge eating disorder

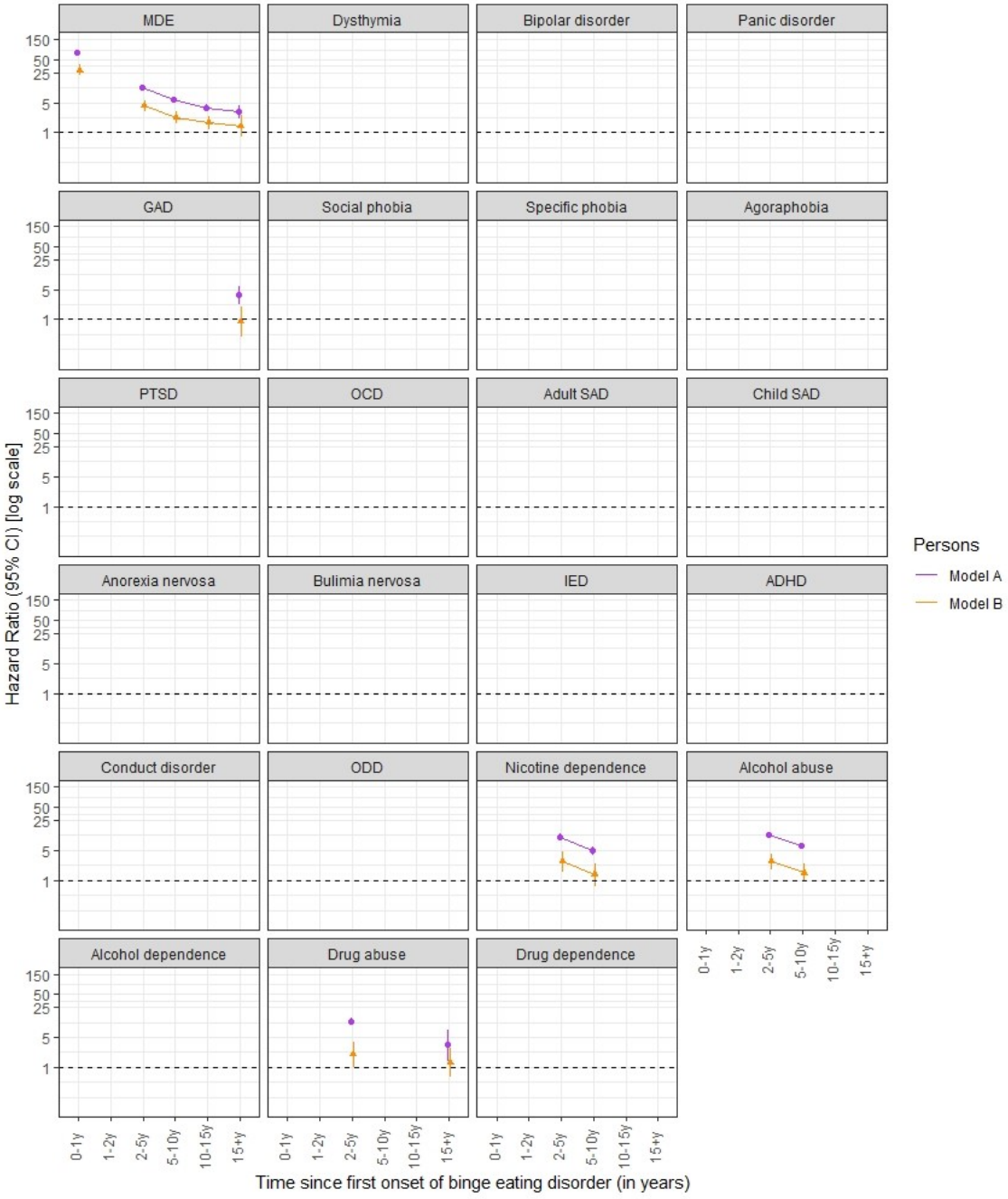


Figure 3p. Risk of later disorders in those with versus those without intermittent explosive disorder

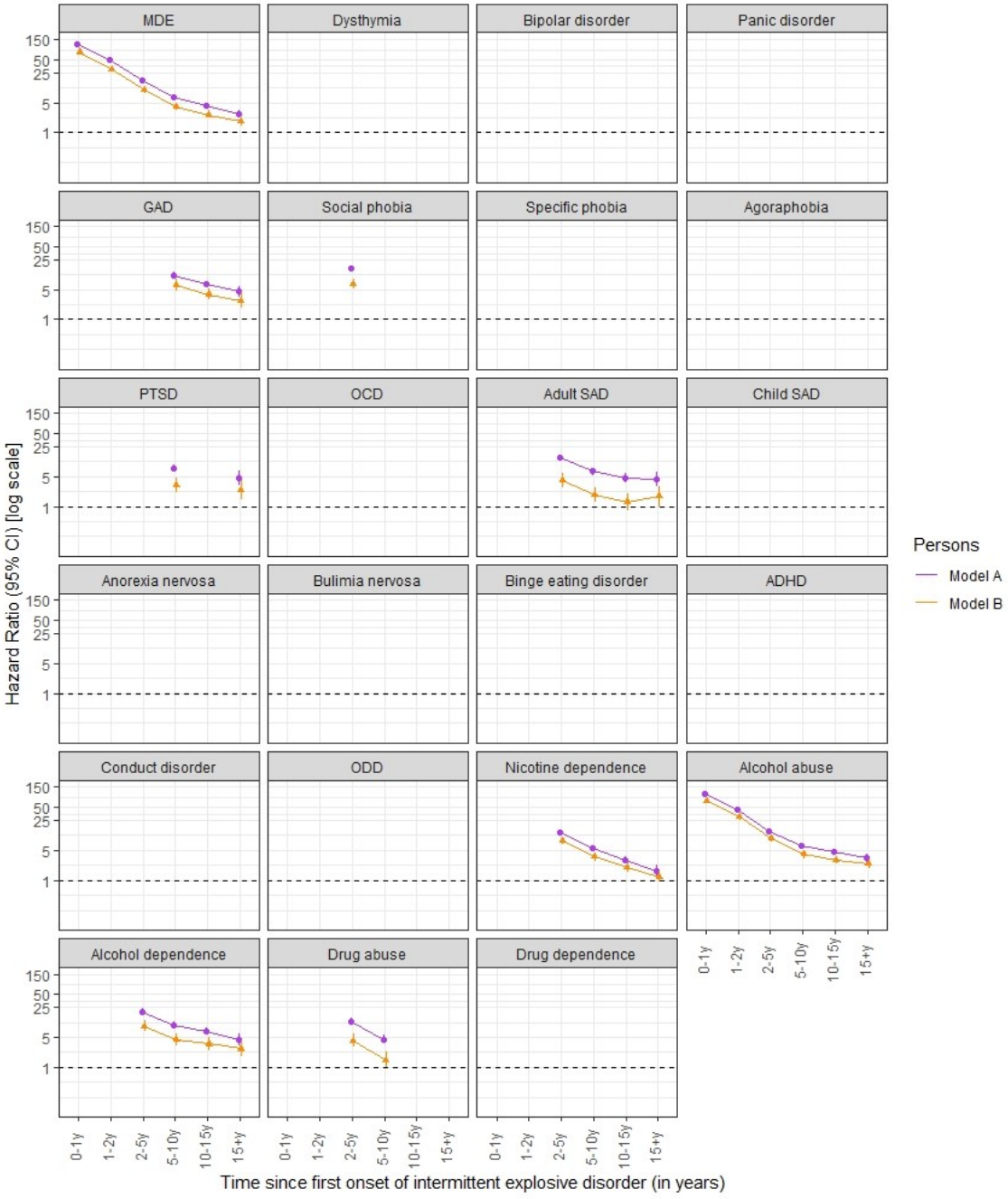


Figure 3q. Risk of later disorders in those with versus those without attention-deficit hyperactivity disorder (ADHD)

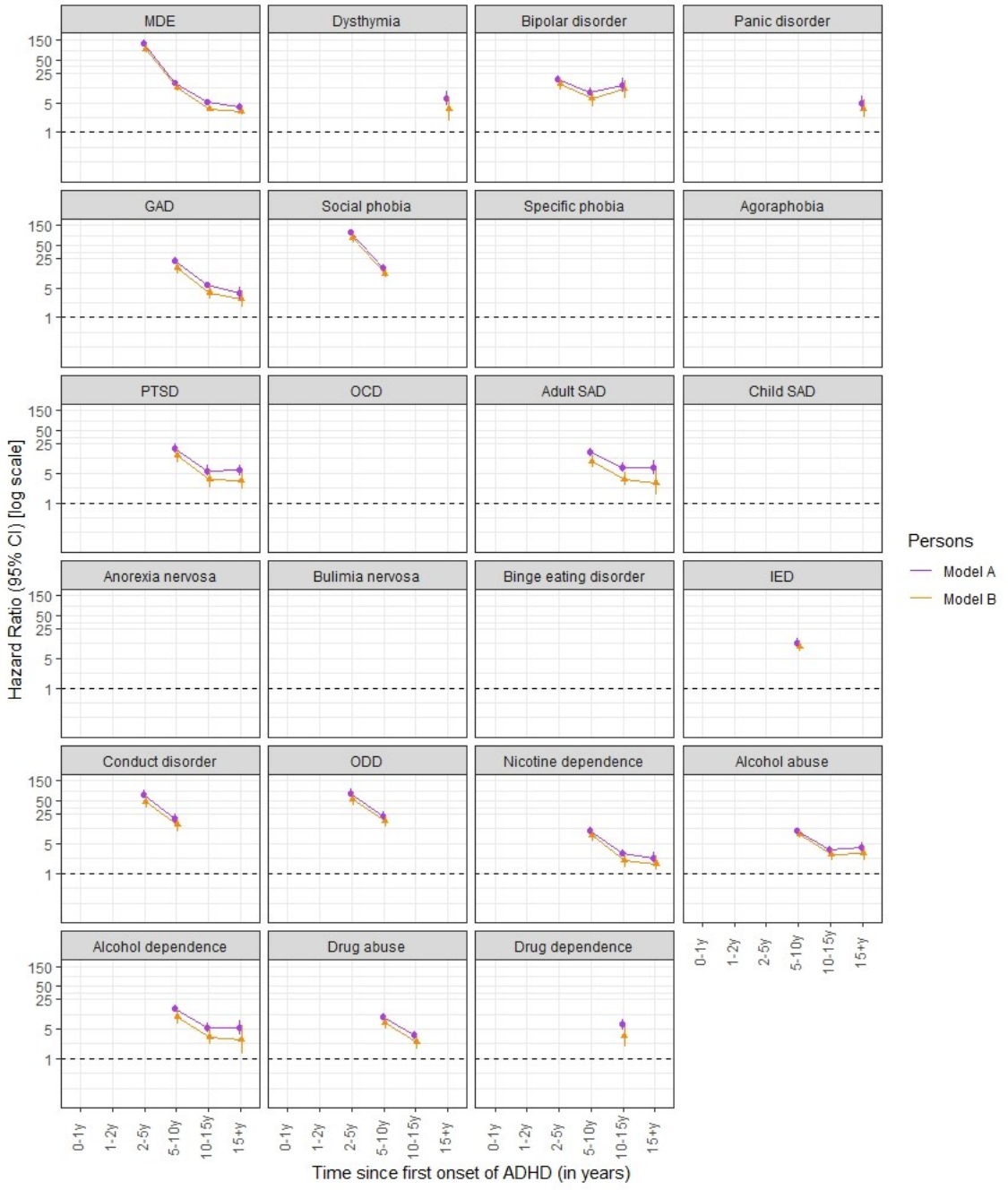


Figure 3r. Risk of later disorders in those with versus those without conduct disorder

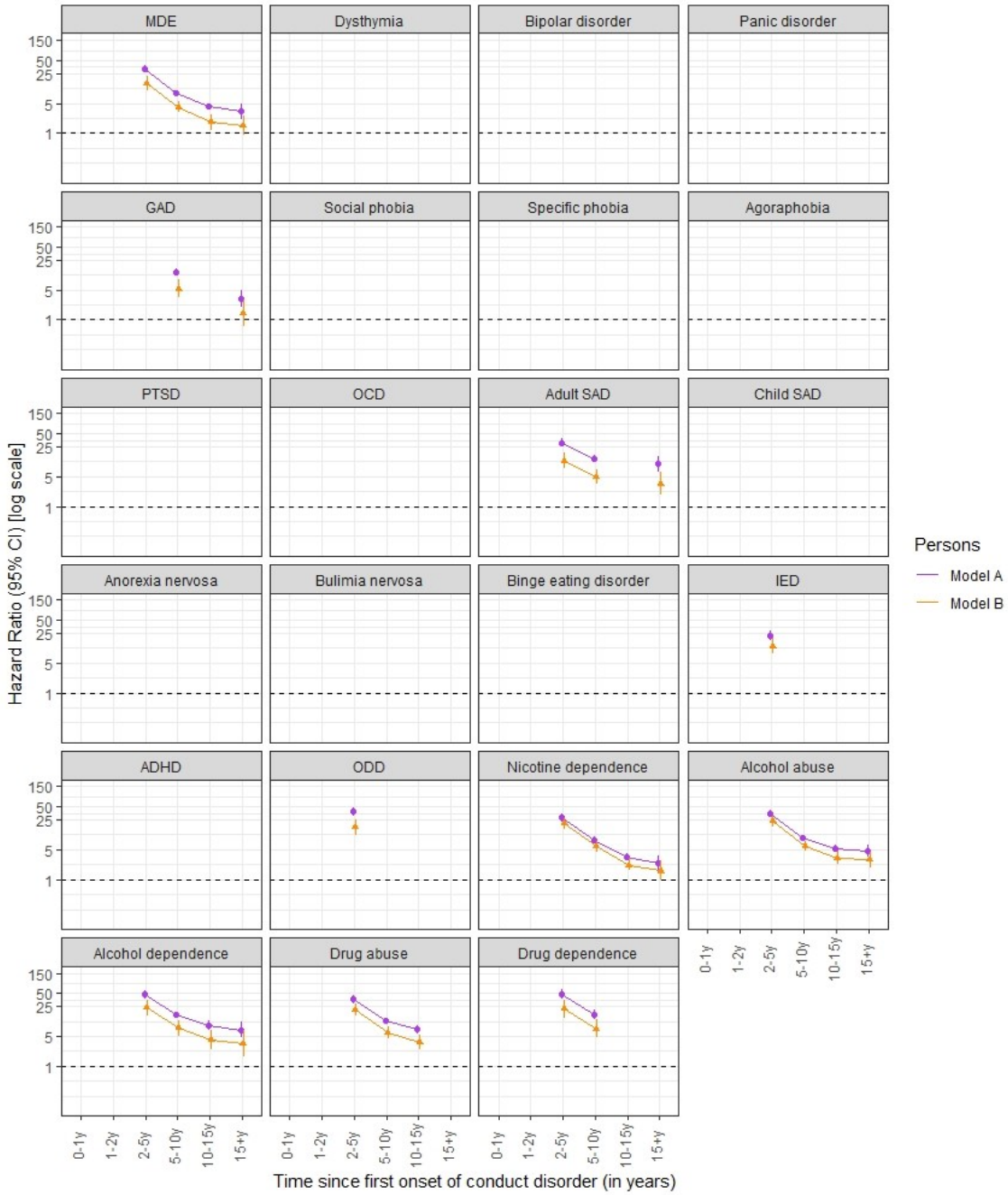


Figure 3s. Risk of later disorders in those with versus those without oppositional defiant disorder

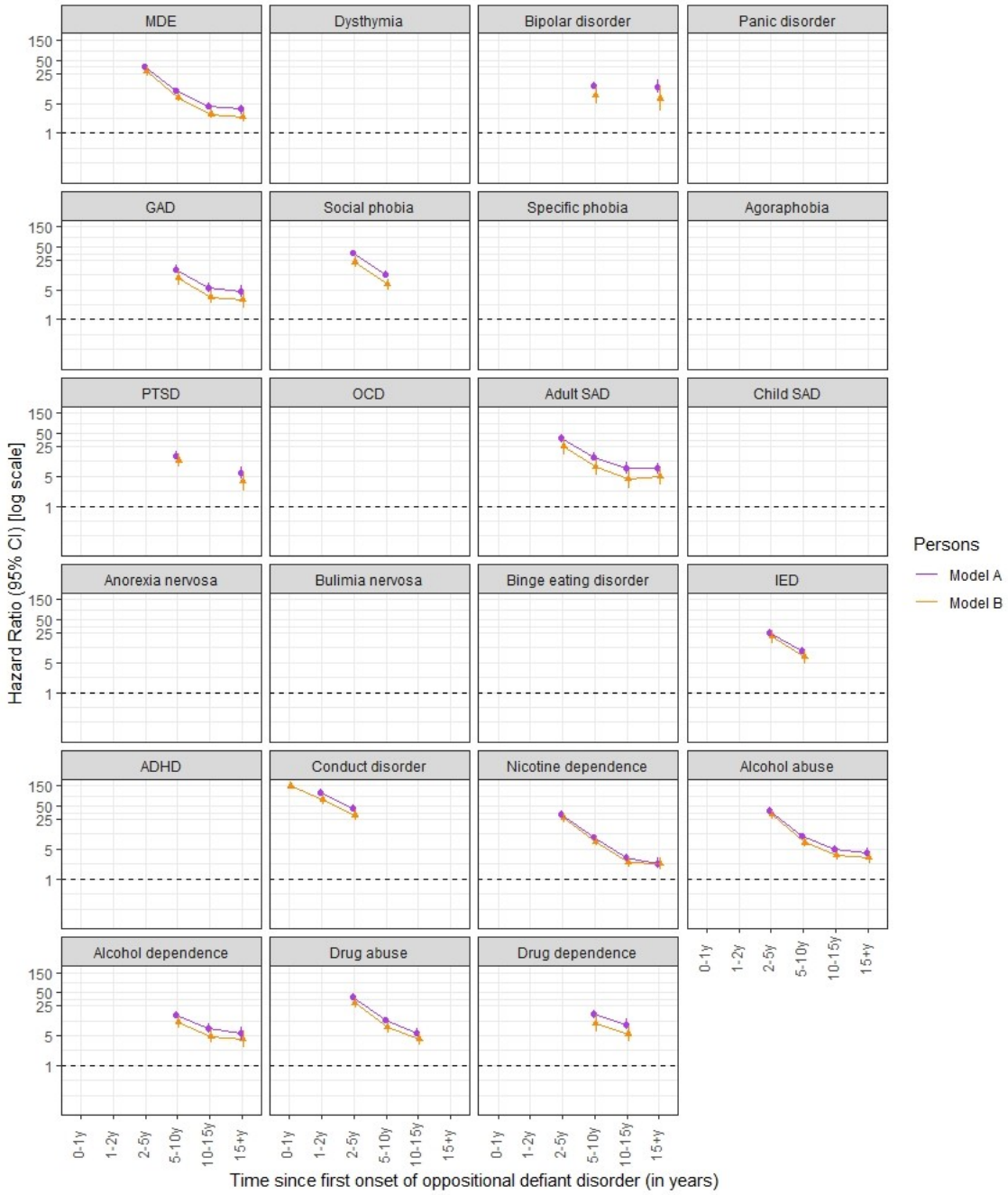


Figure 3t. Risk of later disorders in those with versus those without nicotine dependence

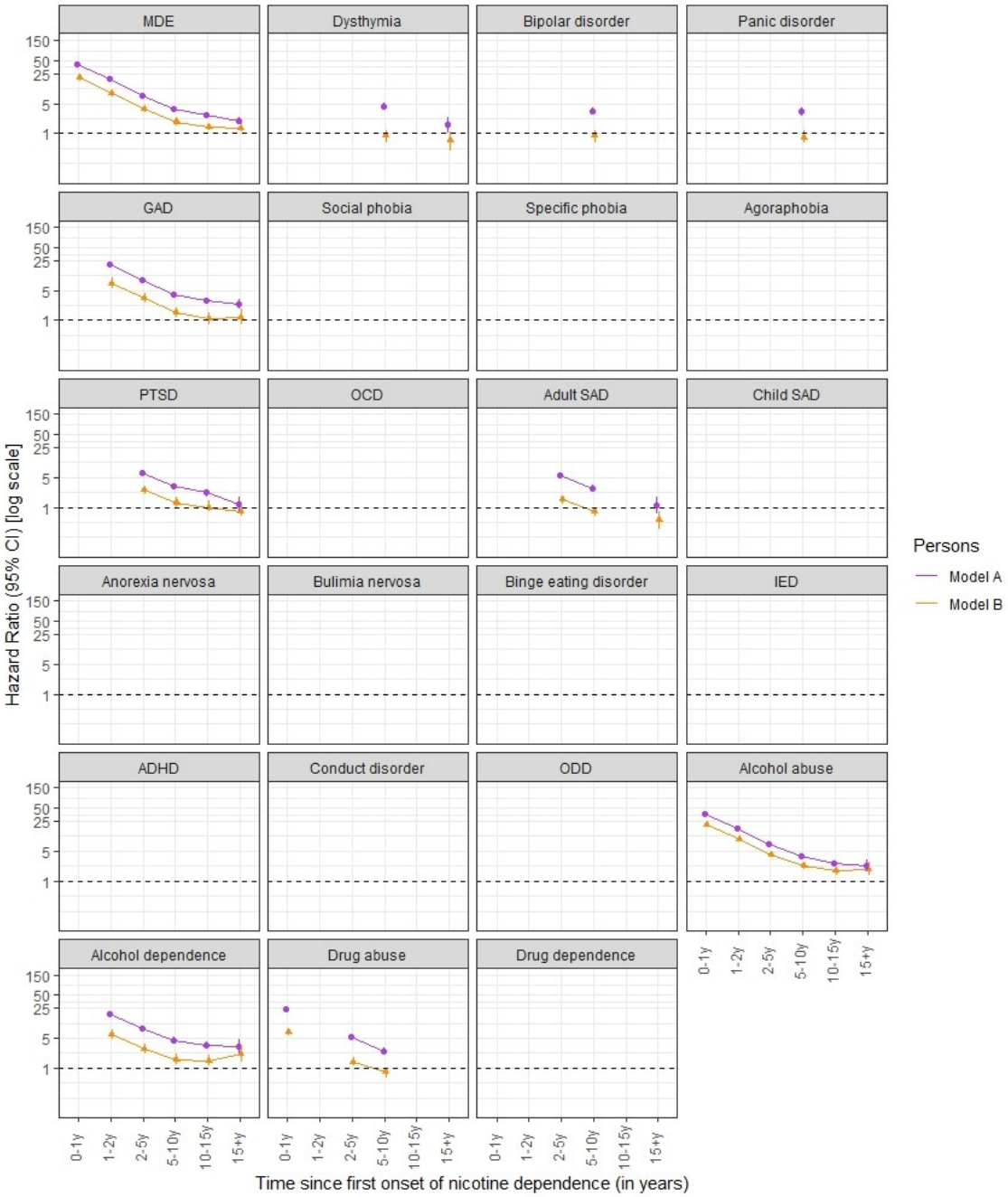


Figure 3u. Risk of later disorders in those with versus those without alcohol abuse

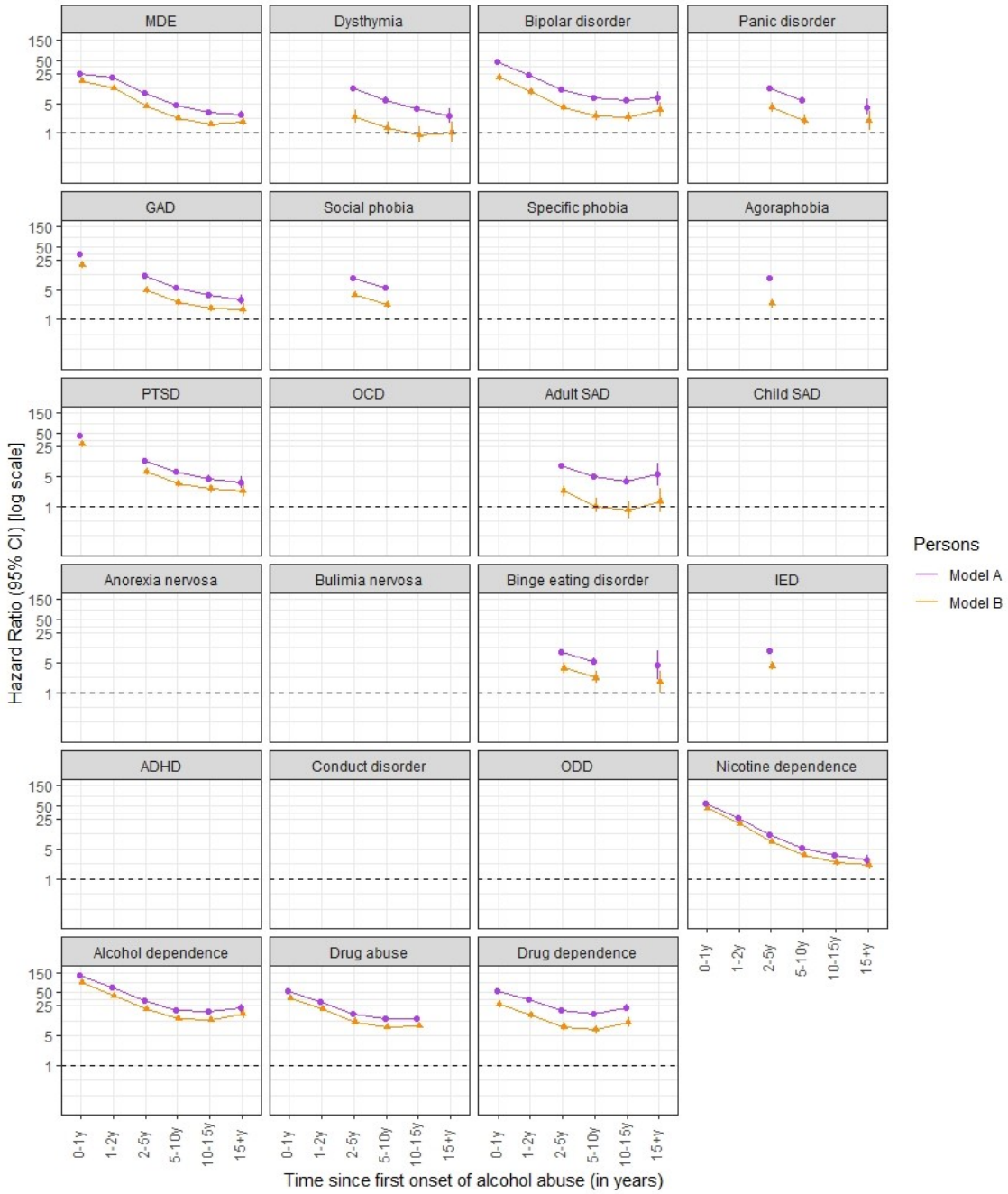


Figure 3v. Risk of later disorders in those with versus those without alcohol dependence

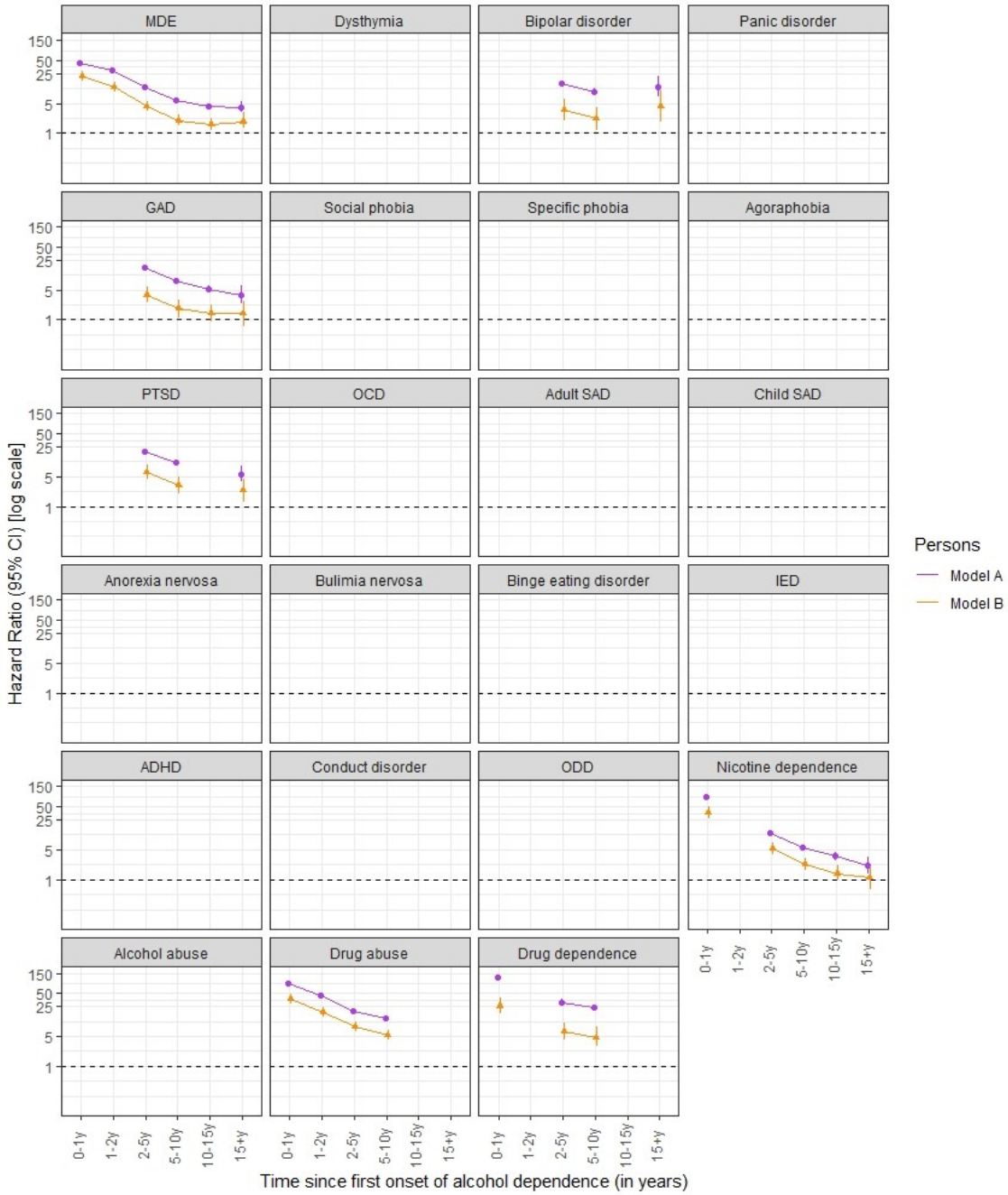


Figure 3w. Risk of later disorders in those with versus those without drug abuse

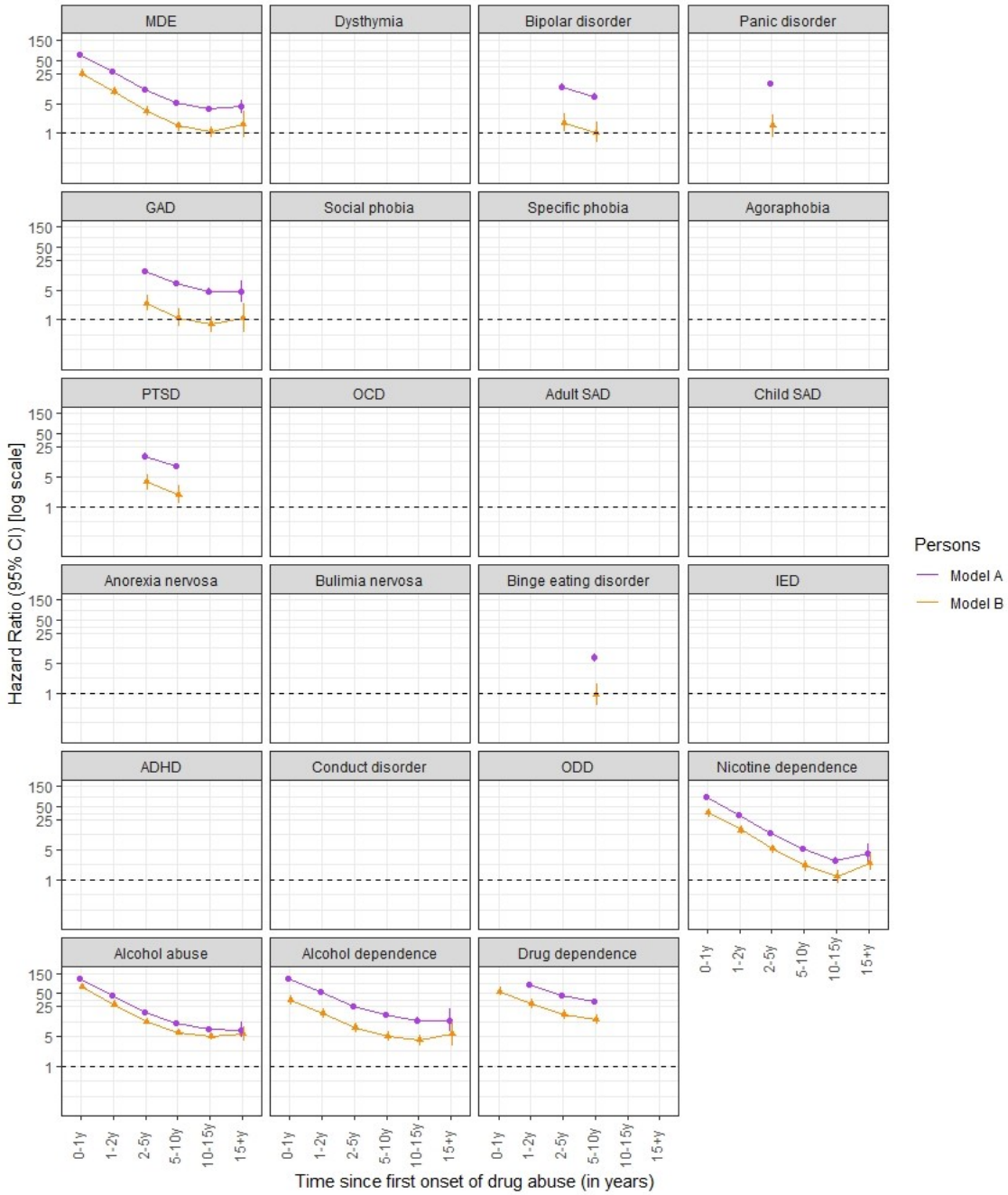
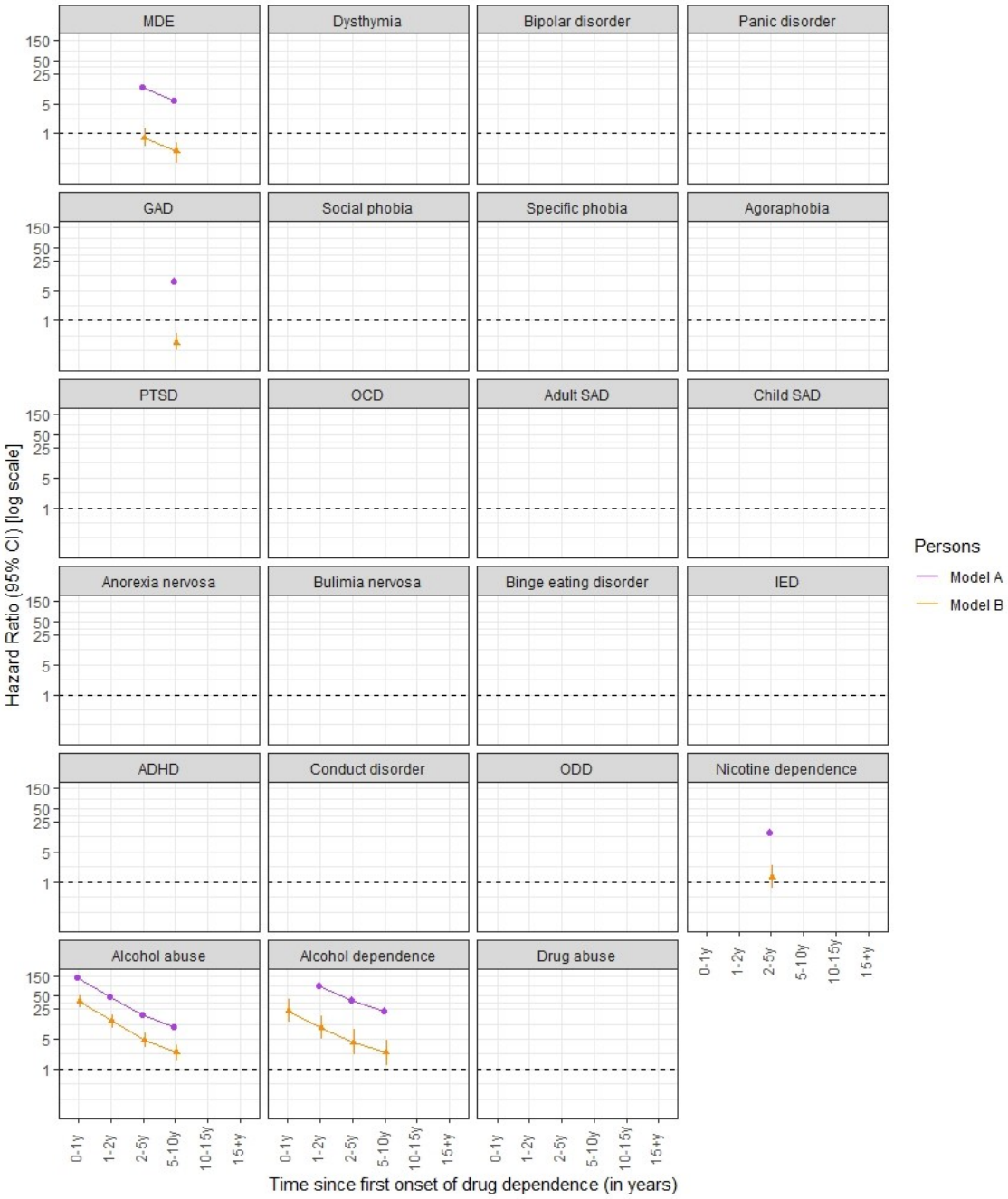


Figure 3x. Risk of later disorders in those with versus those without drug dependence



Supplementary Figure 4. Absolute risks (overall estimate)

Absolute risk of later disorders after the initial onset of a prior disorder

Each panel shows the overall absolute risks (solid orange line) and 95% confidence interval (shaded area) of developing a subsequent later disorder after the onset of prior disorder. The label for each later disorder is shown at the top of each panel. The horizontal axis shows the time since onset of prior disorder. The vertical axis shows the cumulative incidence proportions per 100 persons (and 95% CI). Abbreviations: Major Depressive Episode – MDE; Generalized Anxiety Disorder – GAD; Attention Deficit Hyperactivity Disorder (ADHD); Obsessive Compulsive Disorder (OCD); Post-Traumatic Stress Disorder (PTSD); Separation Anxiety Disorder (SAD); Intermittent Explosive Disorder (IED); Oppositional Defiant Disorder (ODD).

Figure 4a. Absolute risks of later disorder after the initial onset of major depressive episode (MDE)

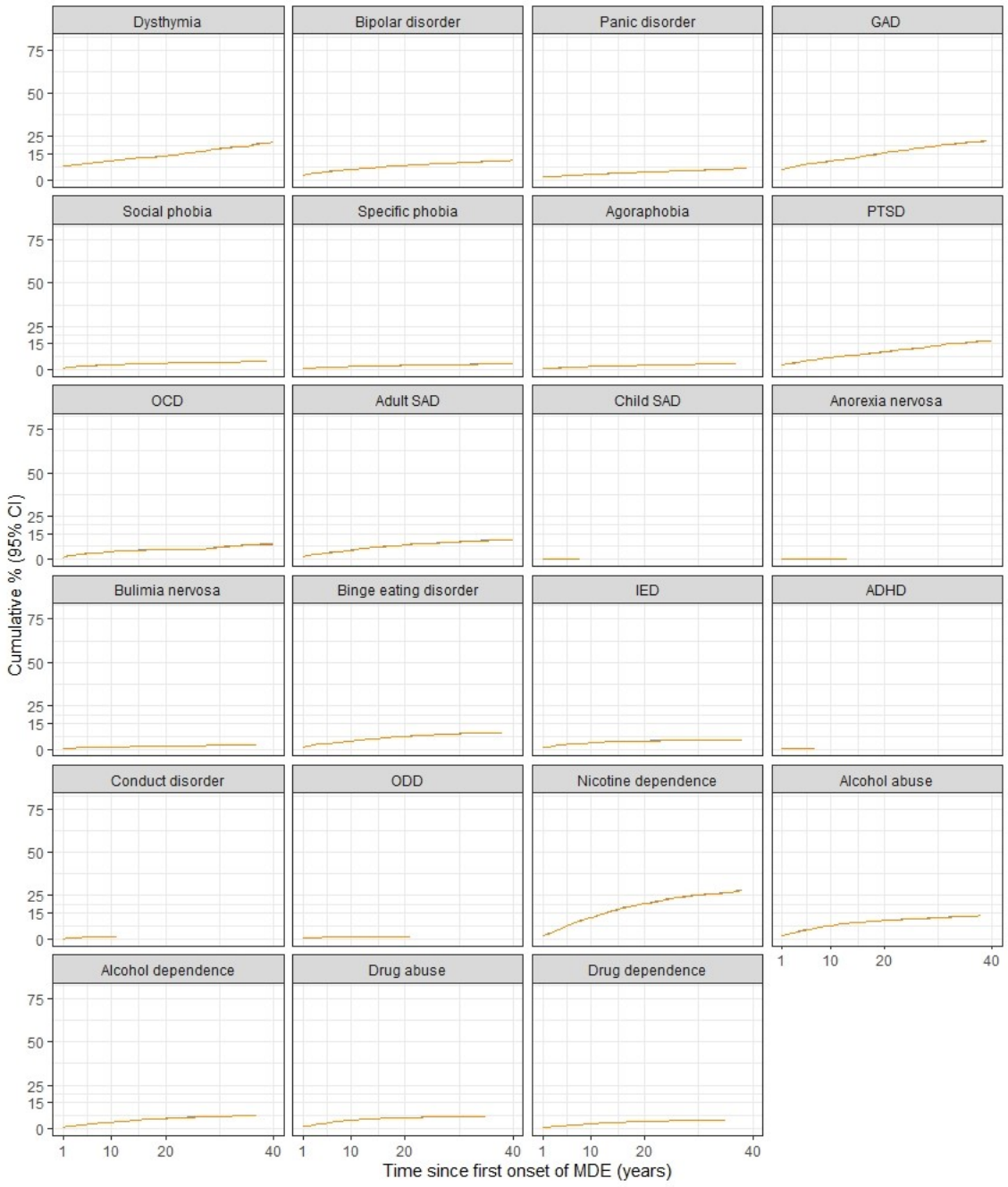


Figure 4b. Absolute risks of later disorders after the initial onset of bipolar disorder

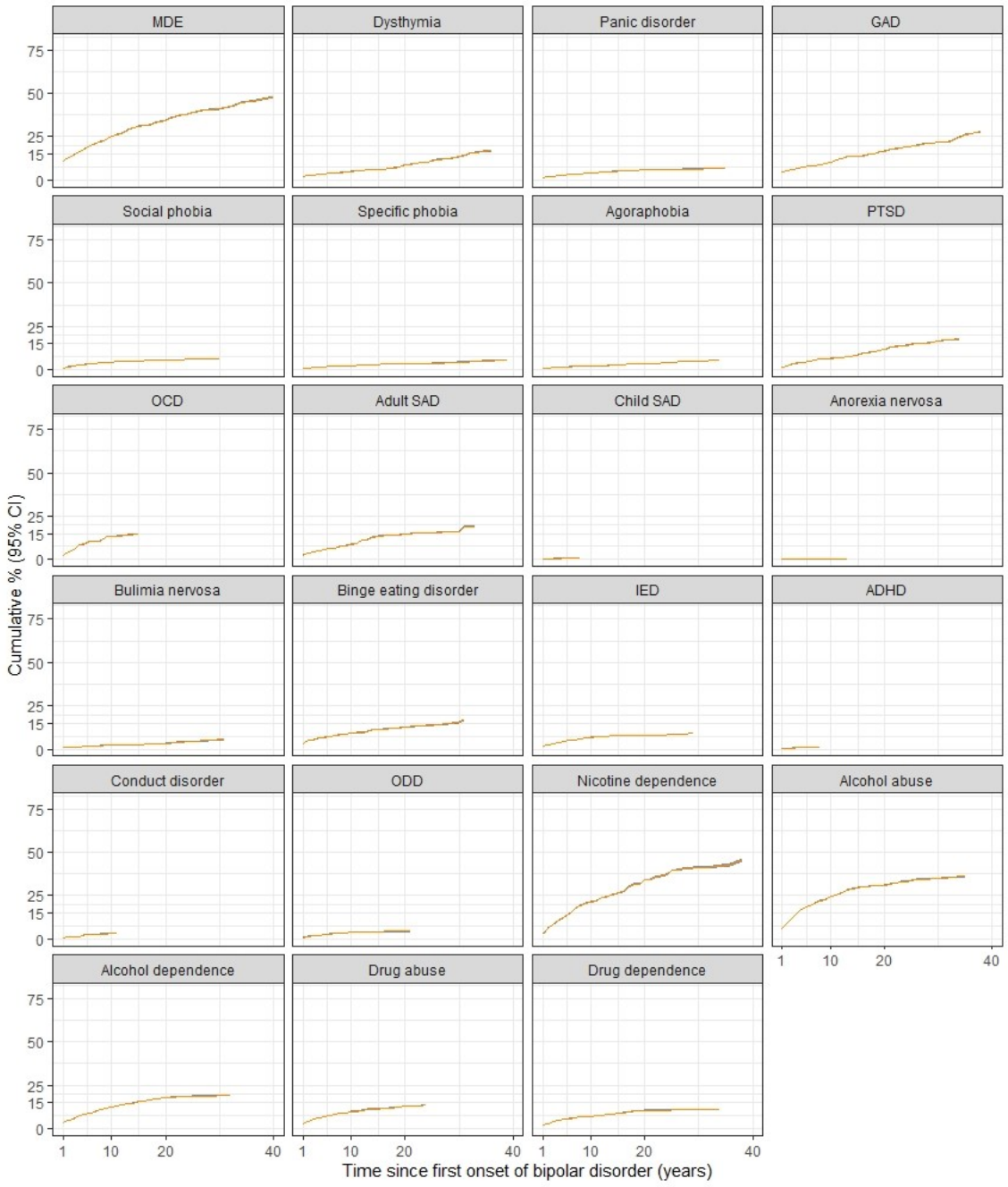


Figure 4c. Absolute risks of later disorders after the initial onset of dysthymia

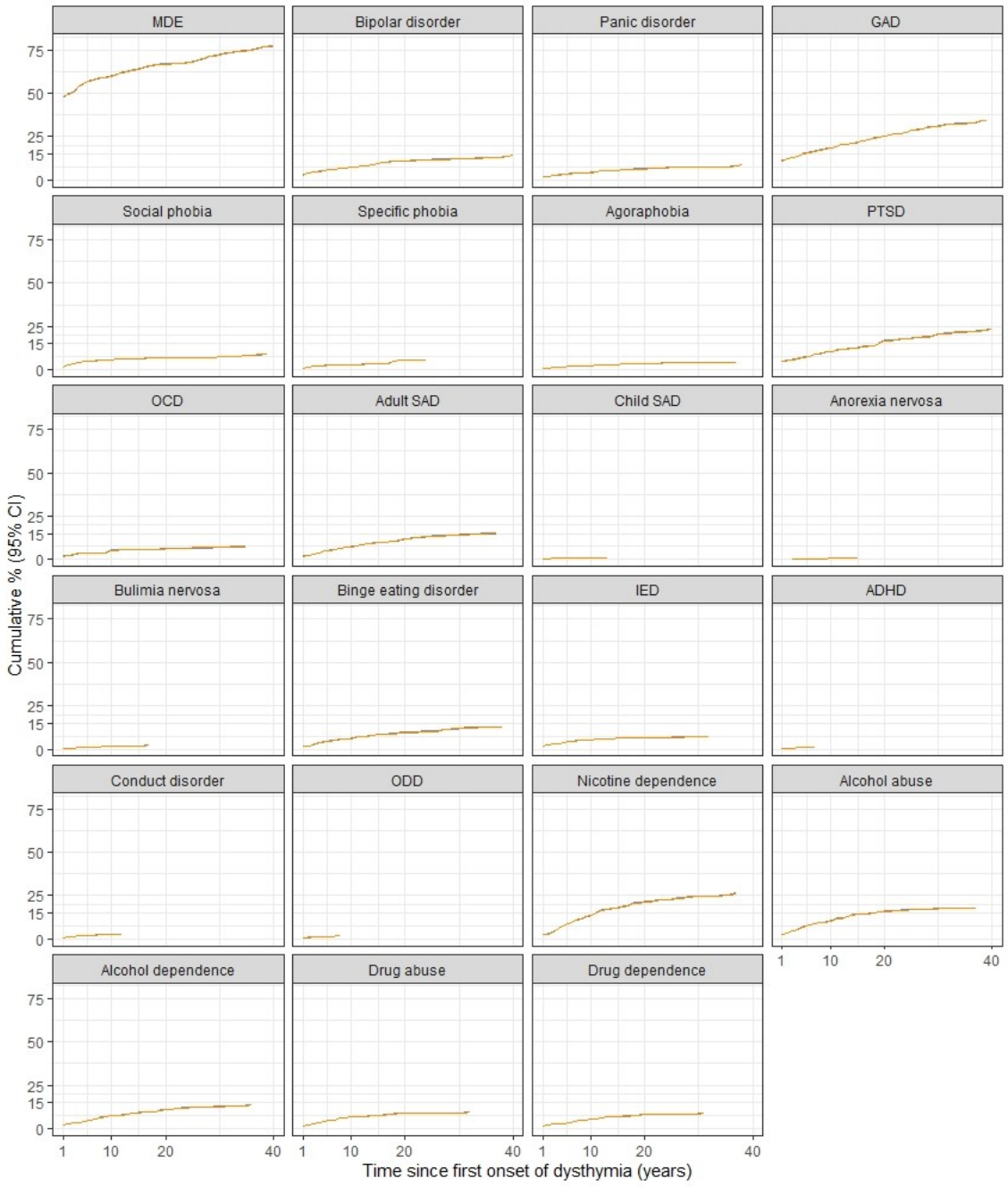


Figure 4d. Absolute risks of later disorders after the initial onset of panic disorder

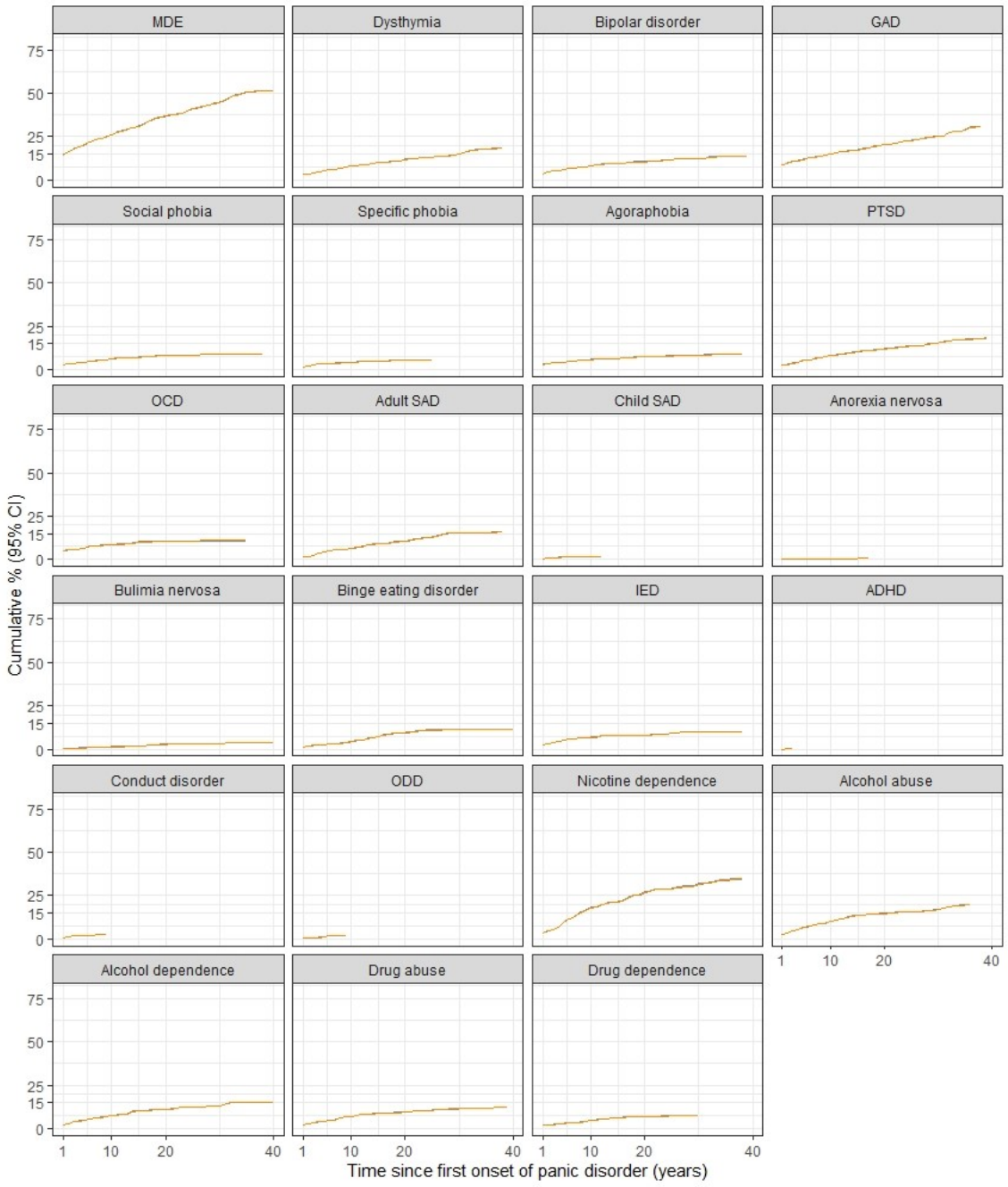


Figure 4e. Absolute risks of later disorders after the initial onset of generalized anxiety disorder (GAD)

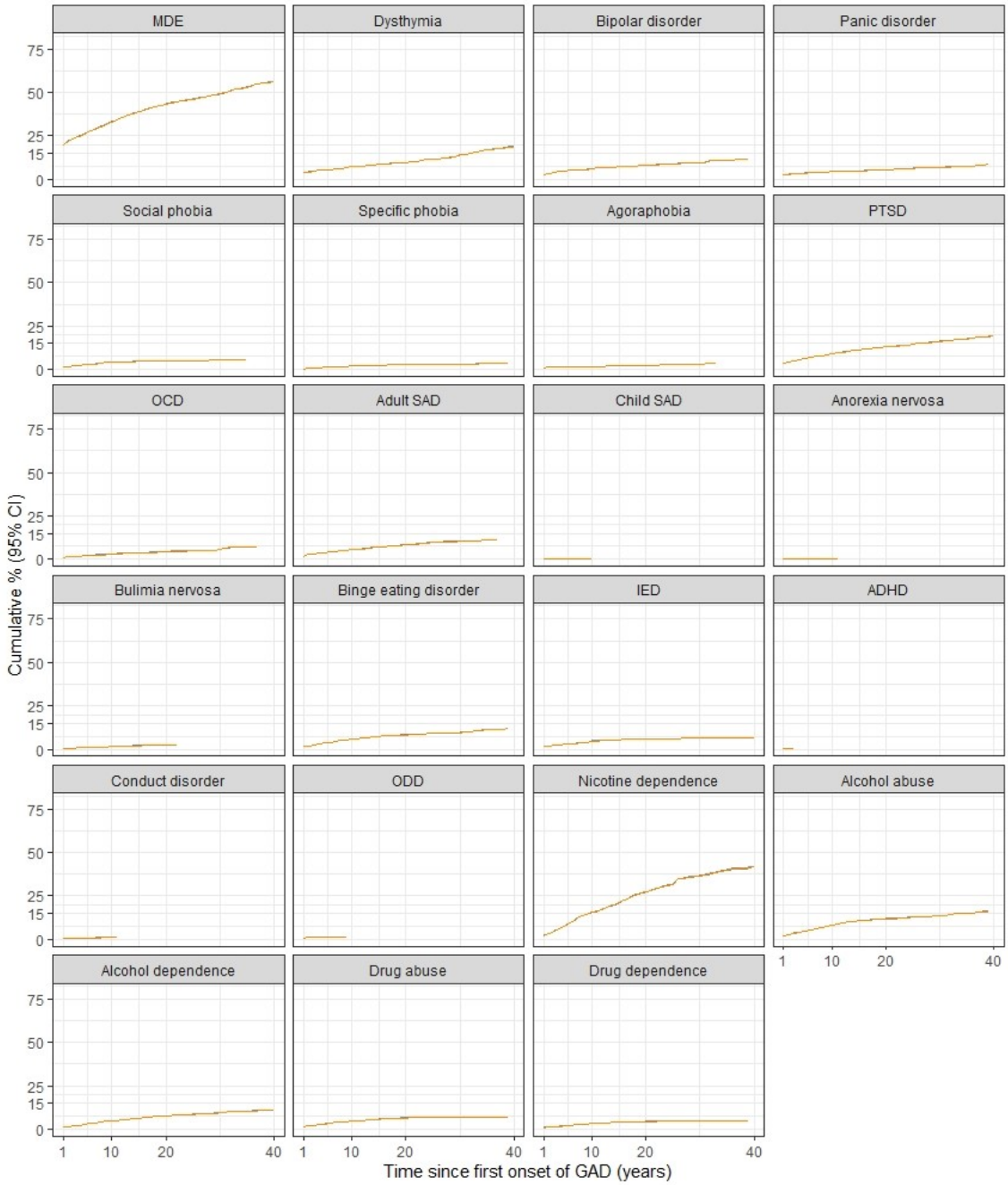


Figure 4f. Absolute risks of later disorders after the initial onset of social phobia

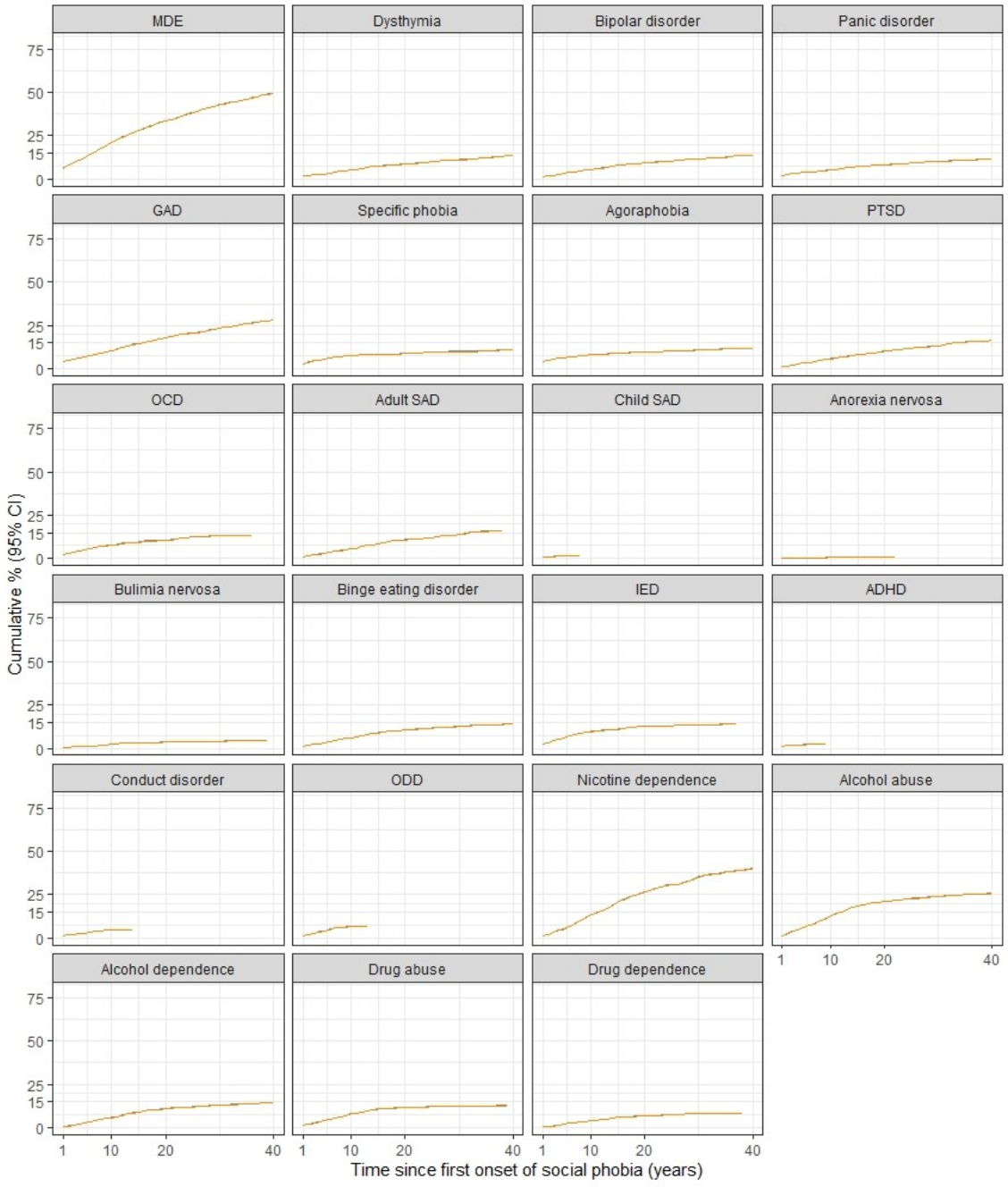


Figure 4g. Absolute risks of later disorders after the initial onset of specific phobia

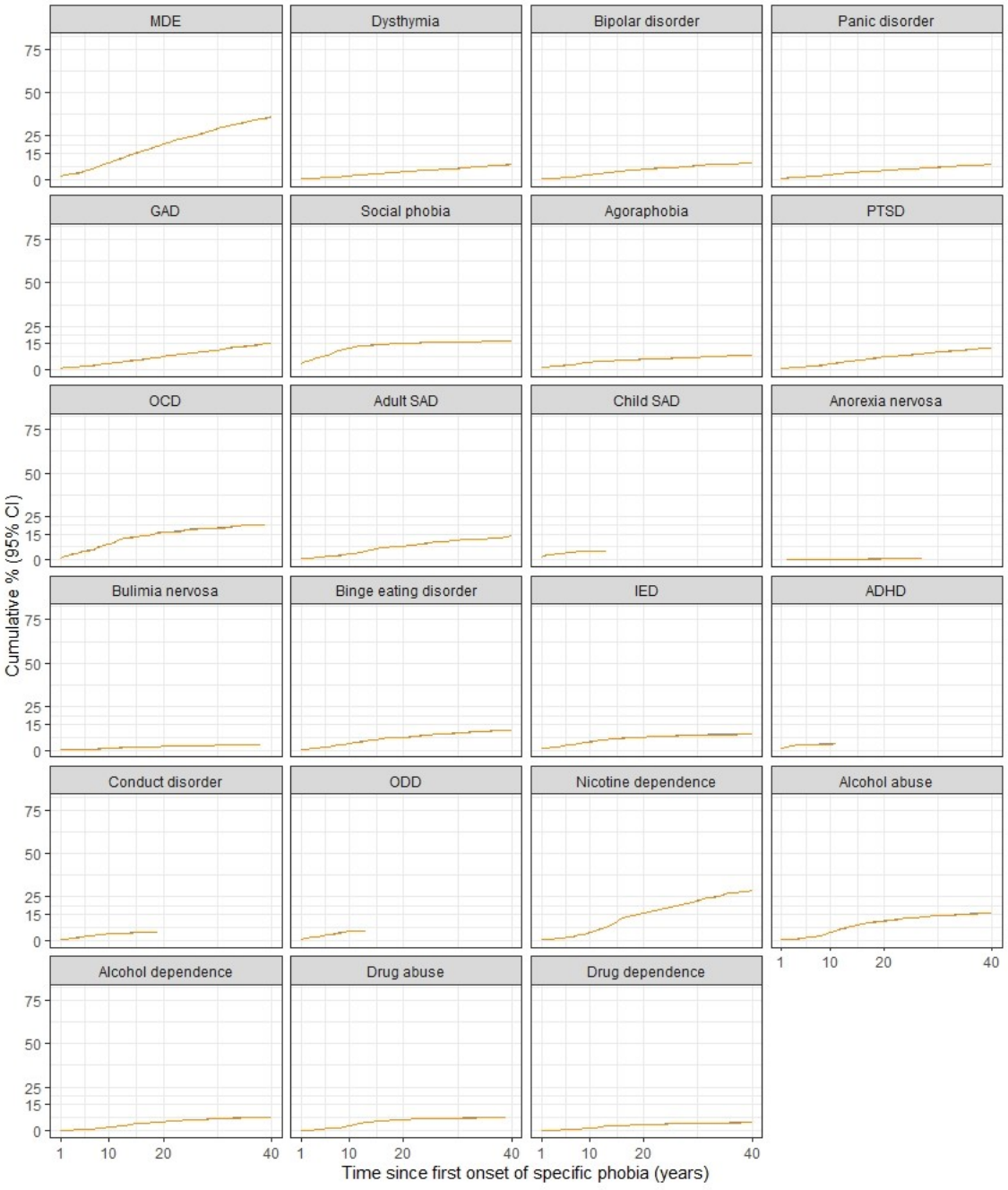


Figure 4h. Absolute risks of later disorders after the initial onset of agoraphobia

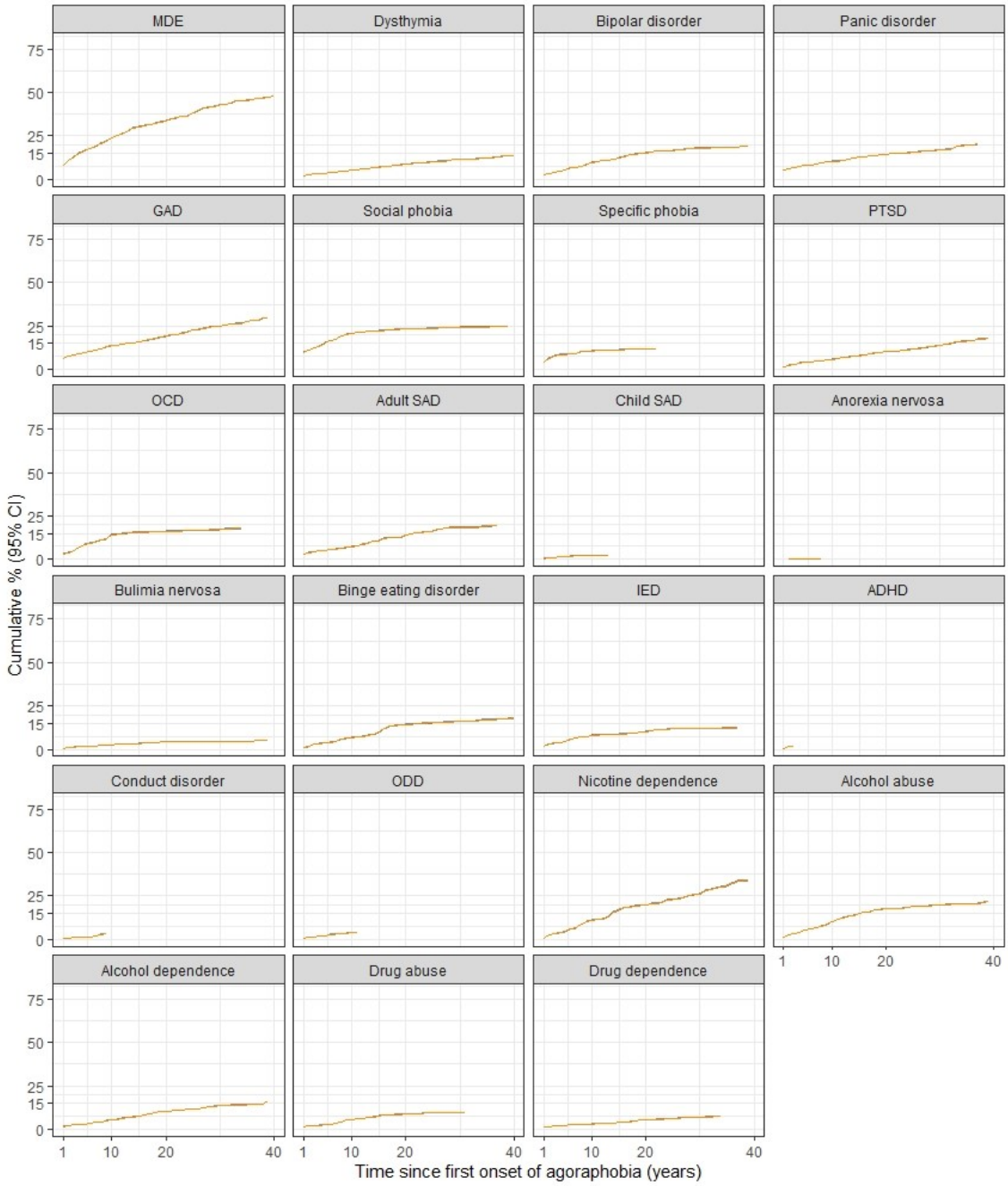


Figure 4i. Absolute risks of later disorders after the initial onset of post-traumatic stress disorder (PTSD)

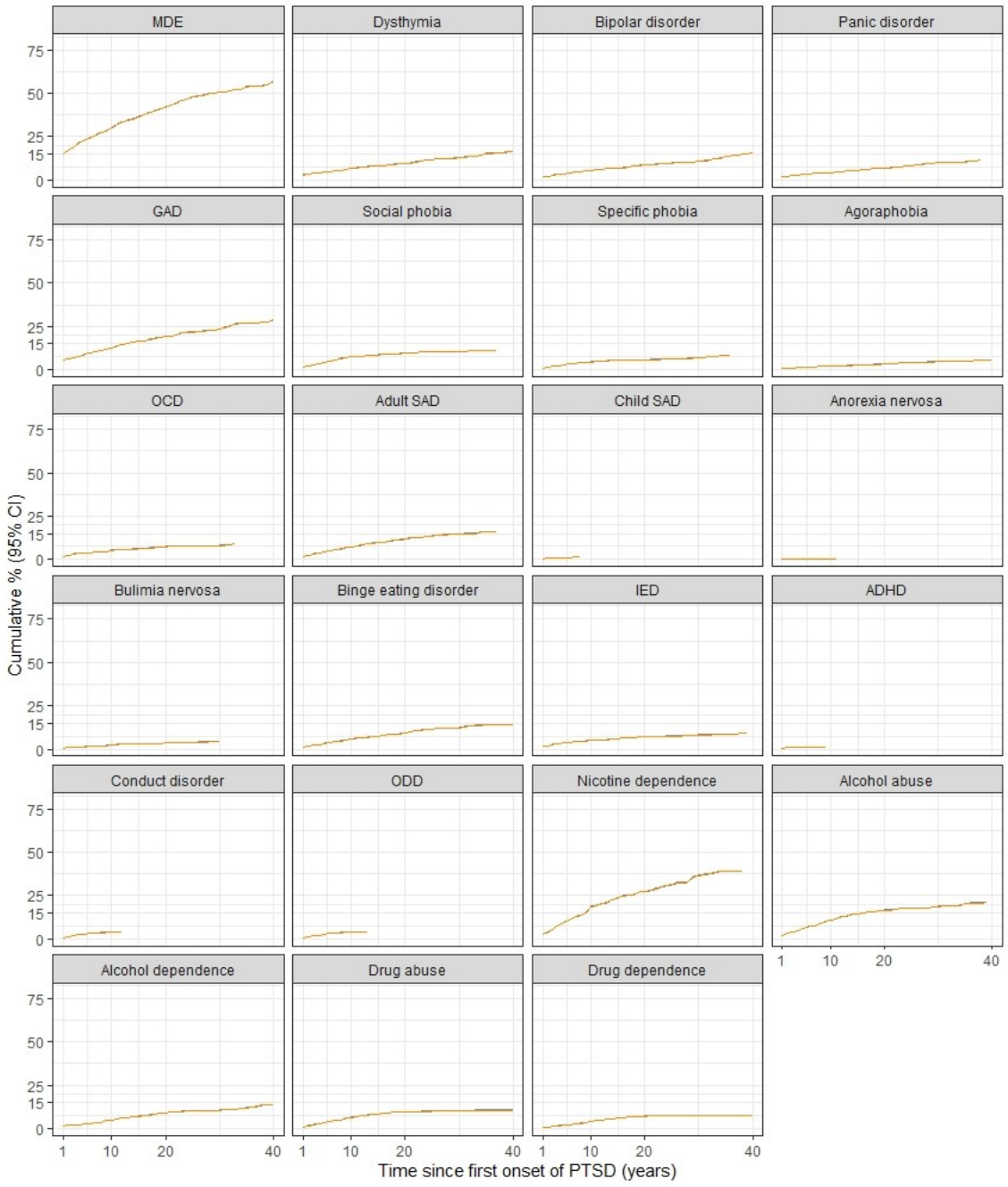


Figure 4j. Absolute risks of later disorders after the initial onset of obsessive compulsive disorder (OCD)

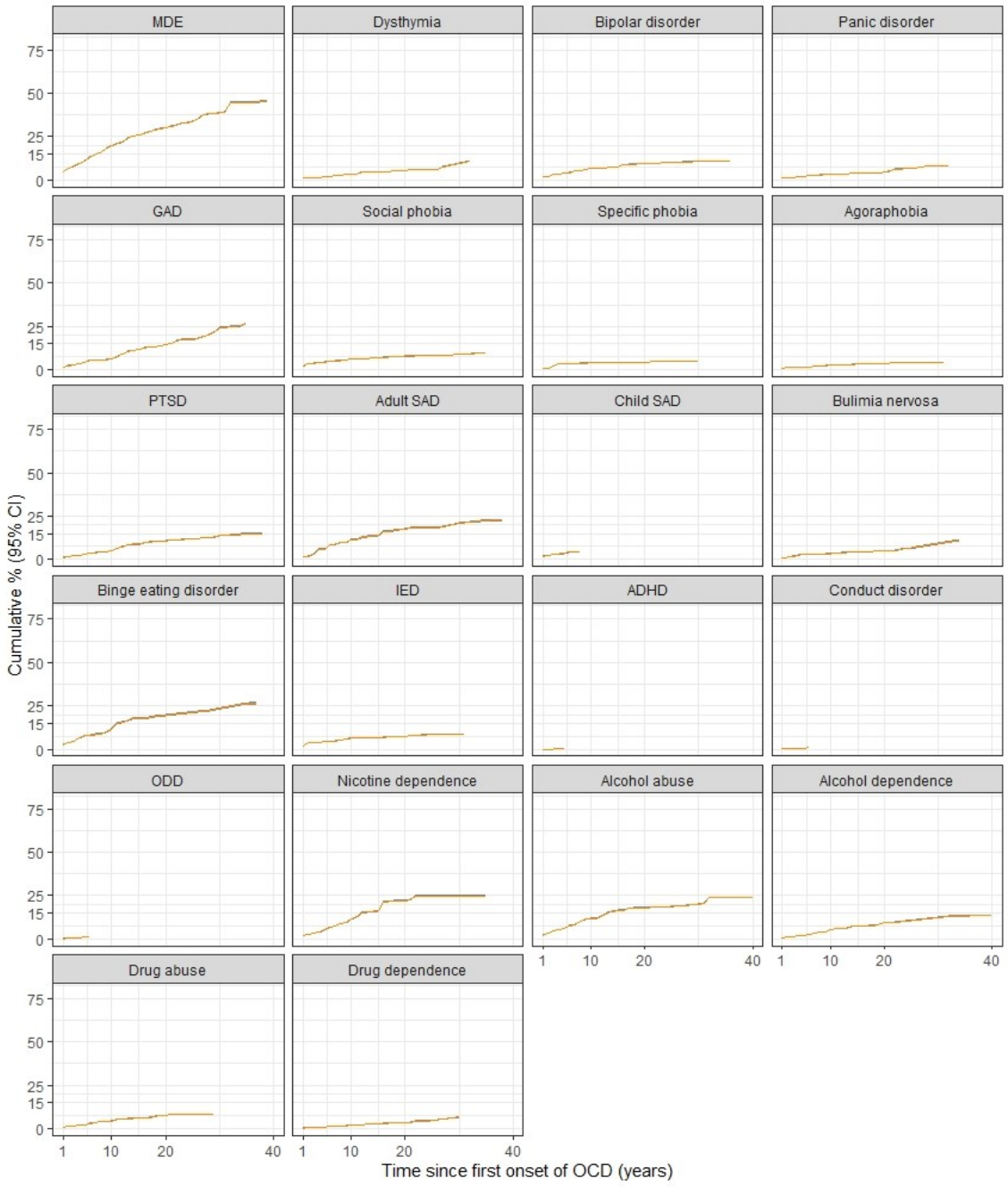


Figure 4k. Absolute risks of later disorders after the initial onset of adult separation anxiety disorder

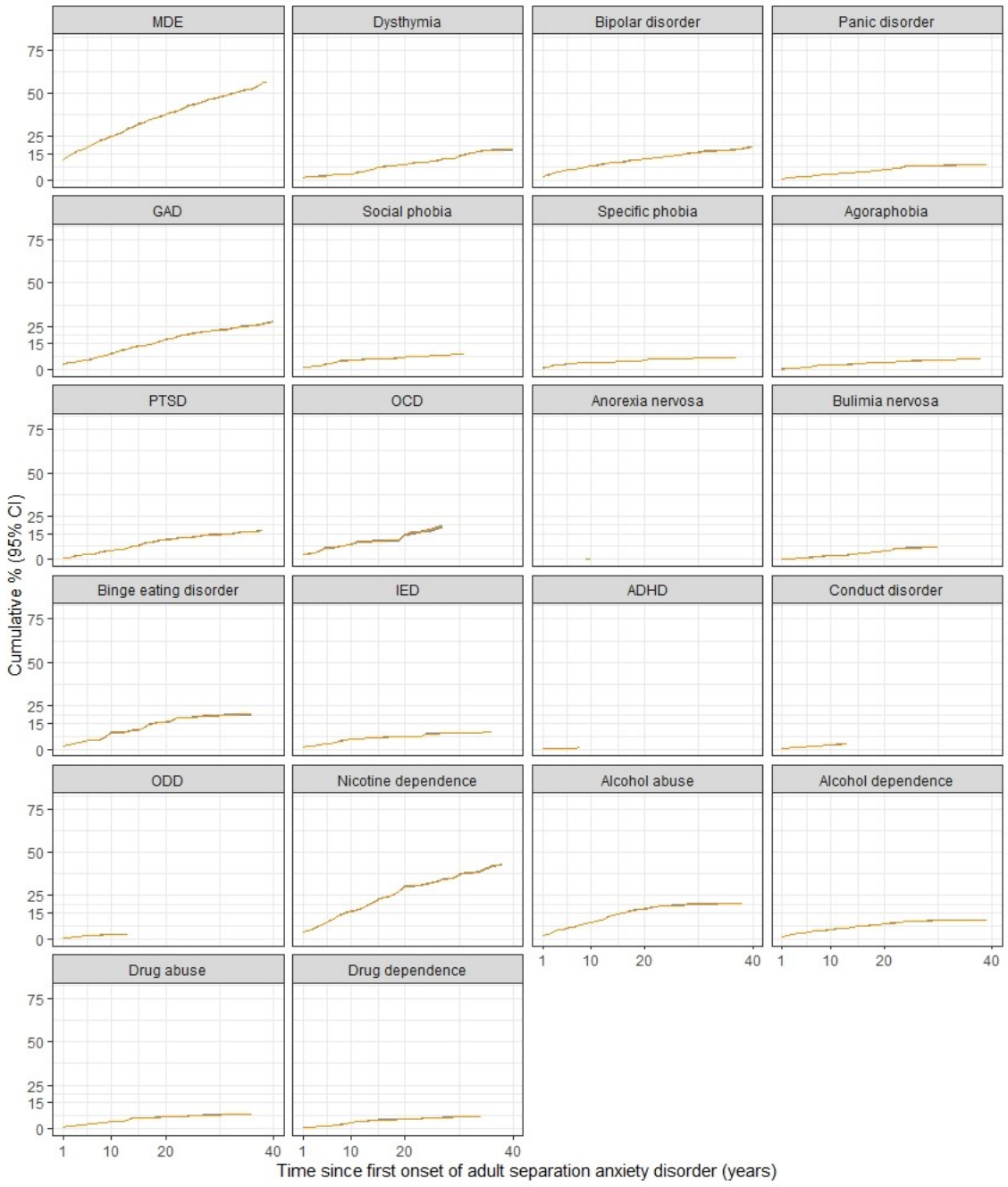


Figure 4l. Absolute risks of later disorders after the initial onset of child separation anxiety disorder

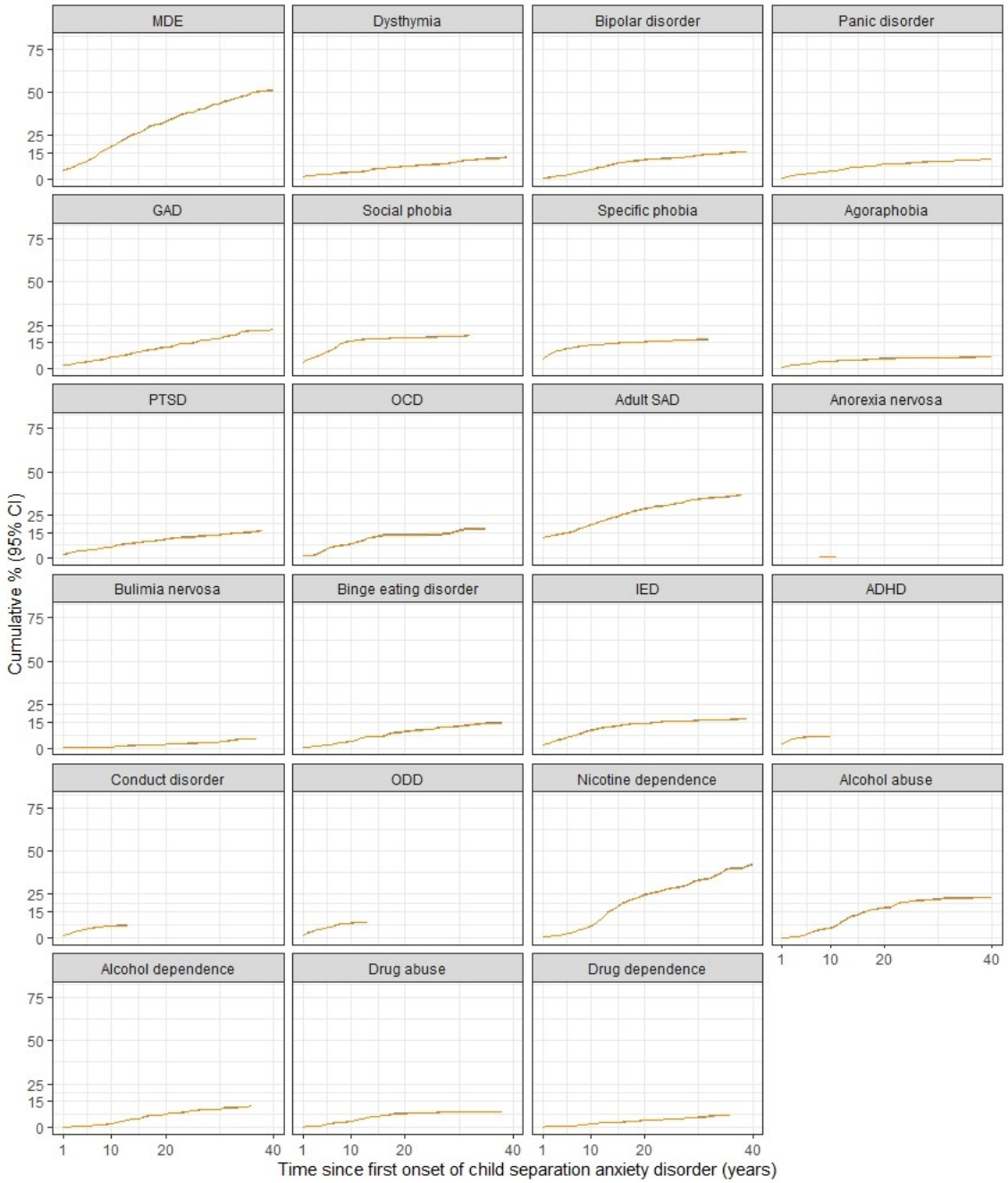


Figure 4m. Absolute risks of later disorders after the initial onset of anorexia nervosa

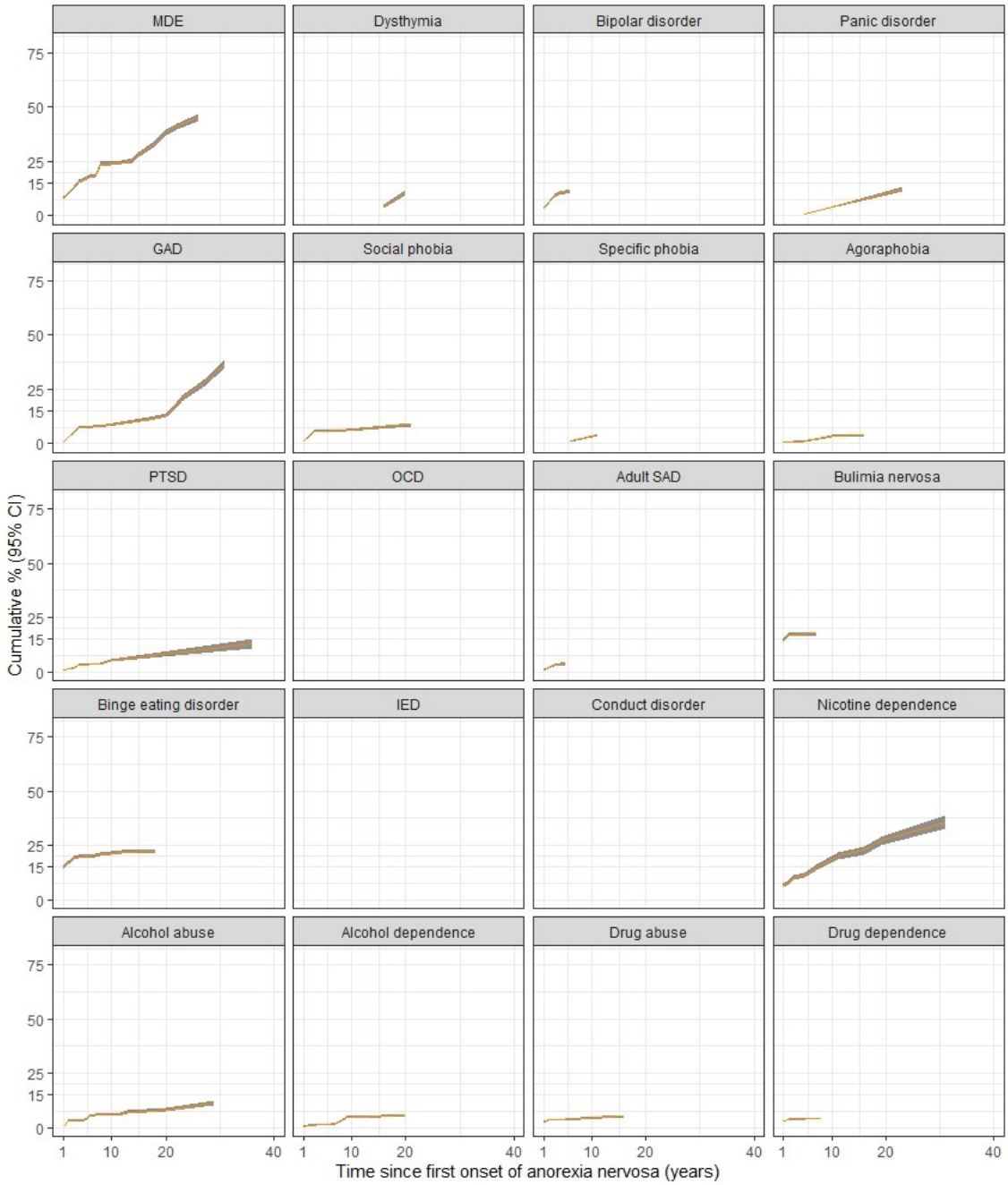


Figure 4n. Absolute risks of later disorders after the initial onset of bulimia nervosa

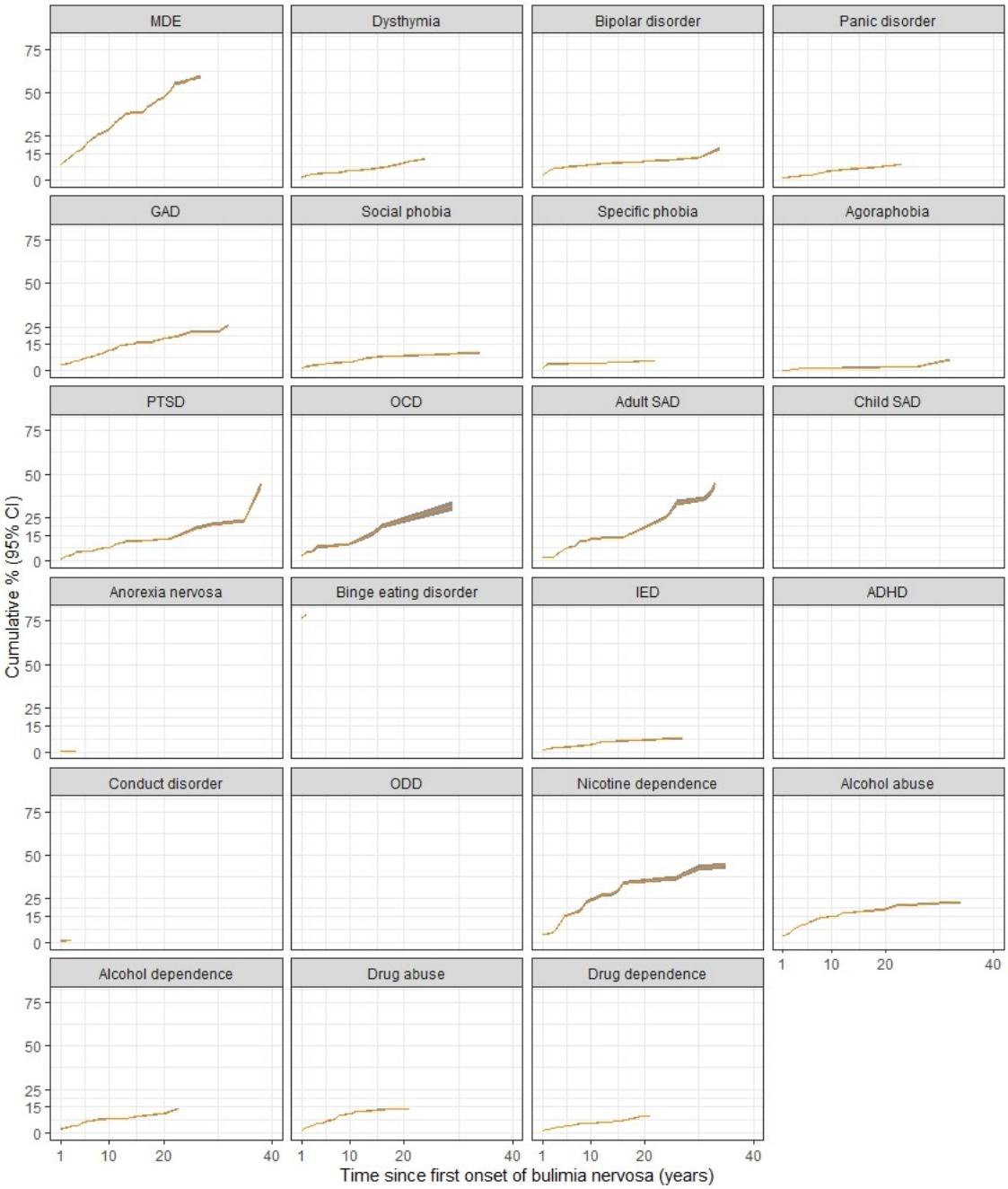


Figure 4o. Absolute risks of later disorders after the initial onset of binge eating disorder

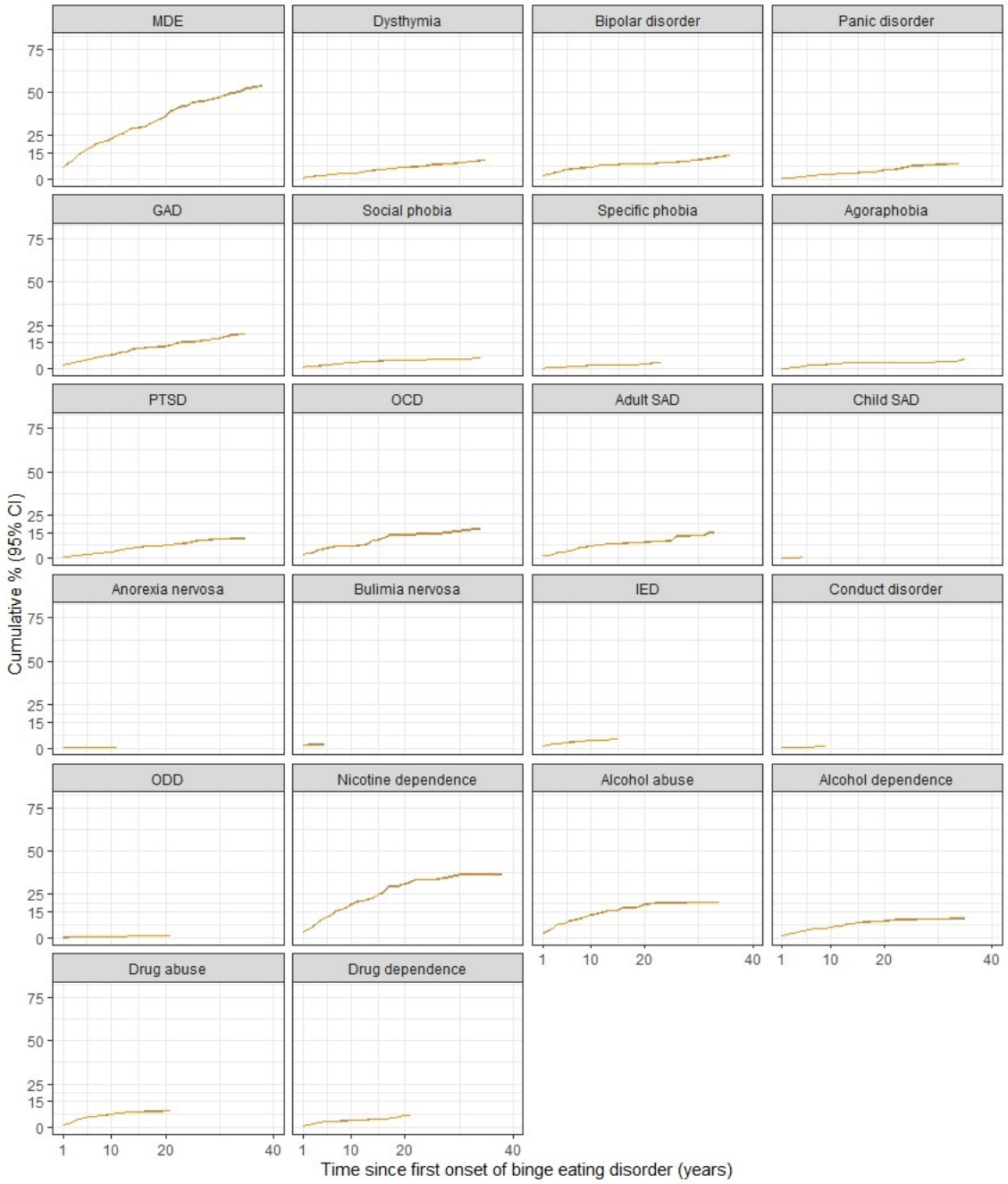


Figure 4p. Absolute risks of later disorders after the initial onset of intermittent explosive disorder (IED)

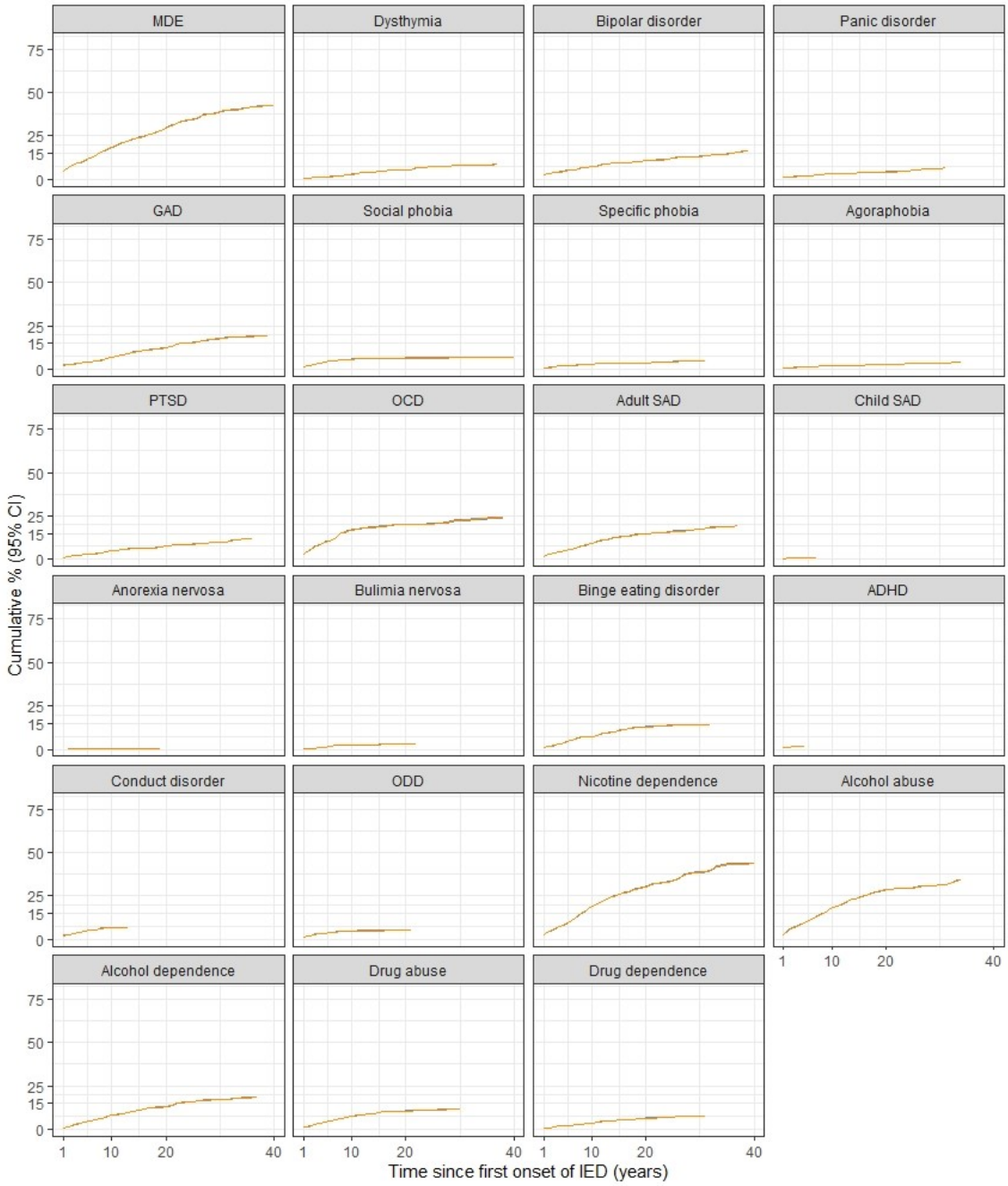


Figure 4q. Absolute risks of later disorders after the initial onset of attention-deficit hyperactivity disorder (ADHD)

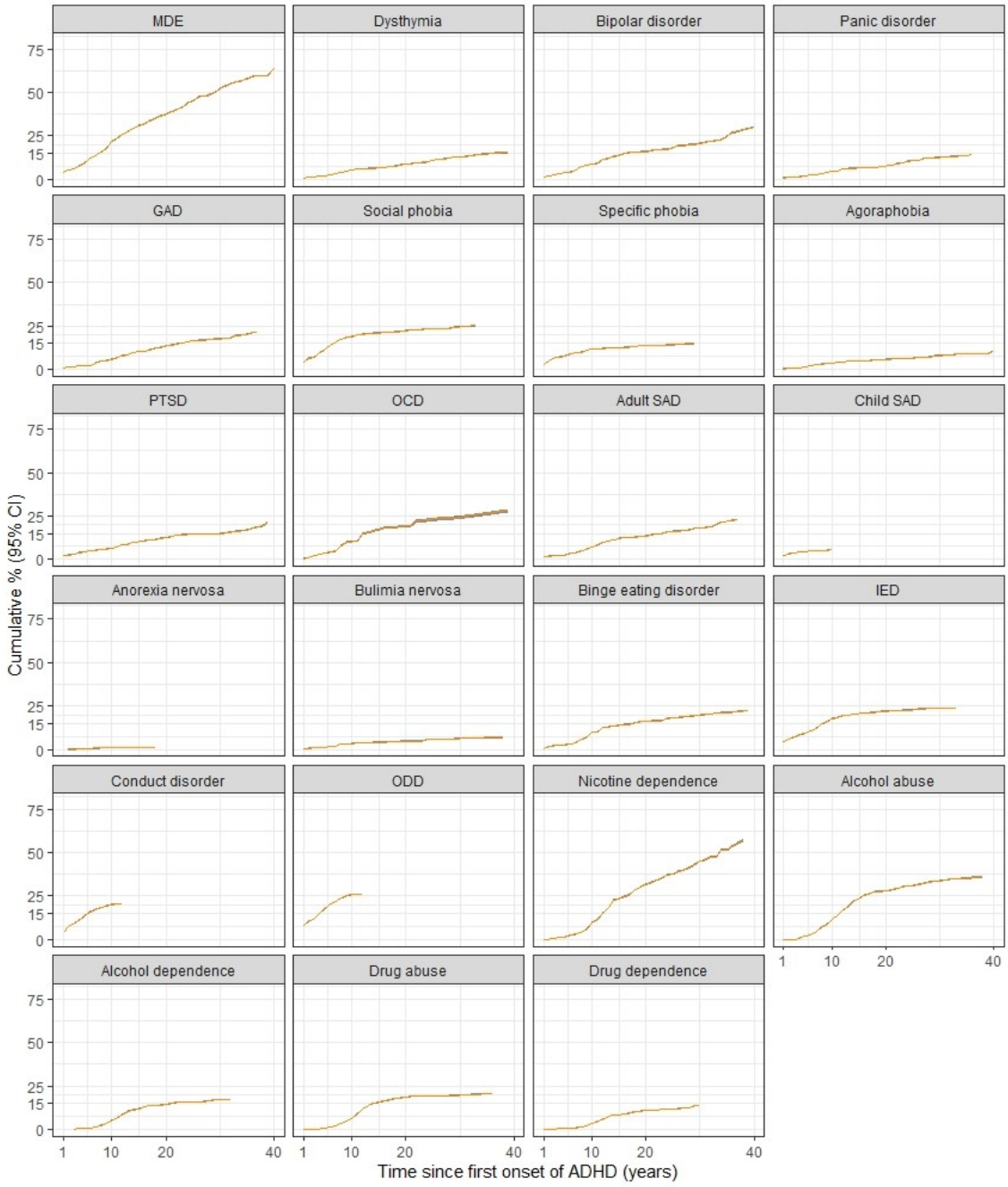


Figure 4r. Absolute risks of later disorders after the initial onset of conduct disorder

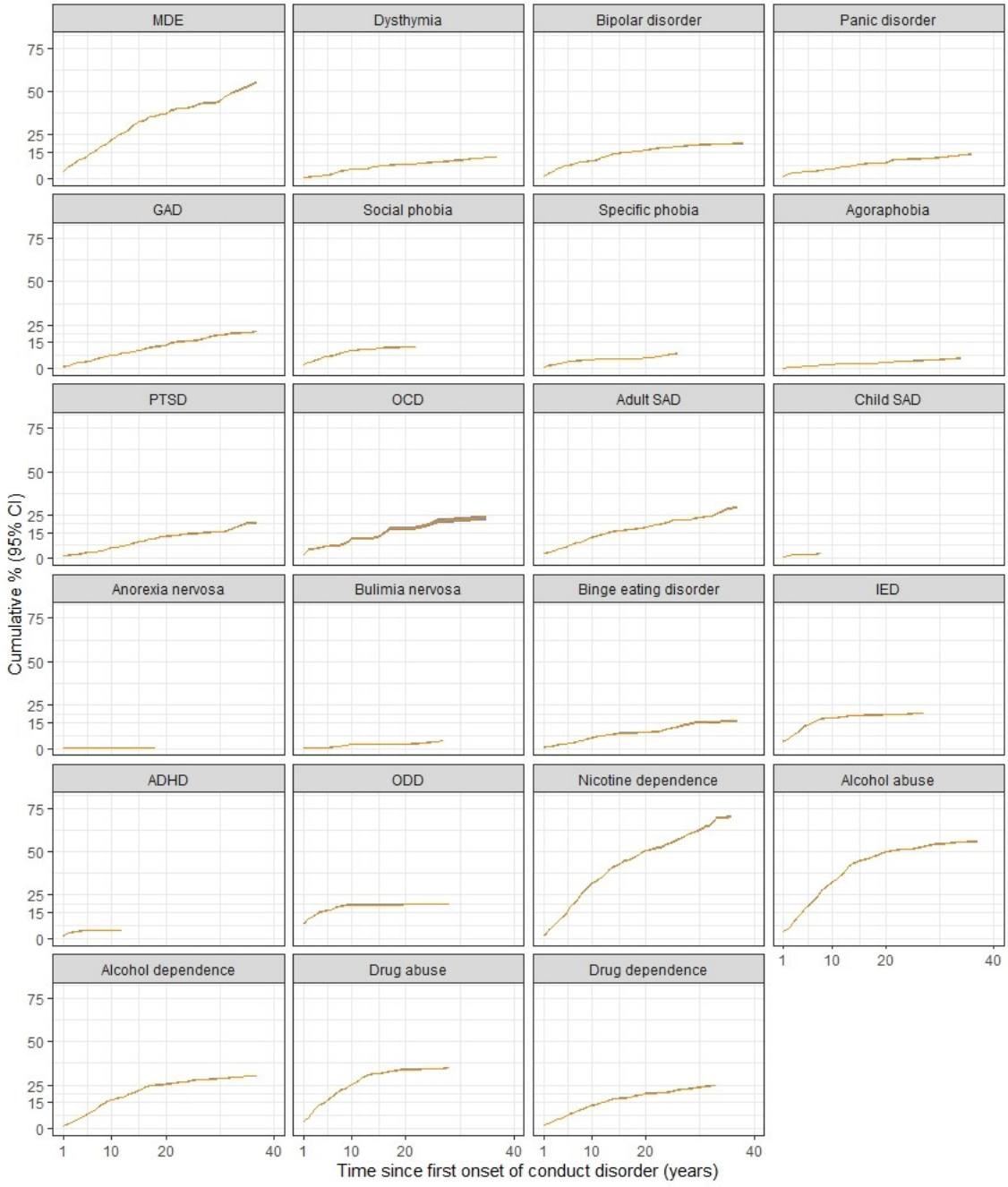


Figure 4s. Absolute risks of later disorders after the initial onset of oppositional defiant disorder (ODD)

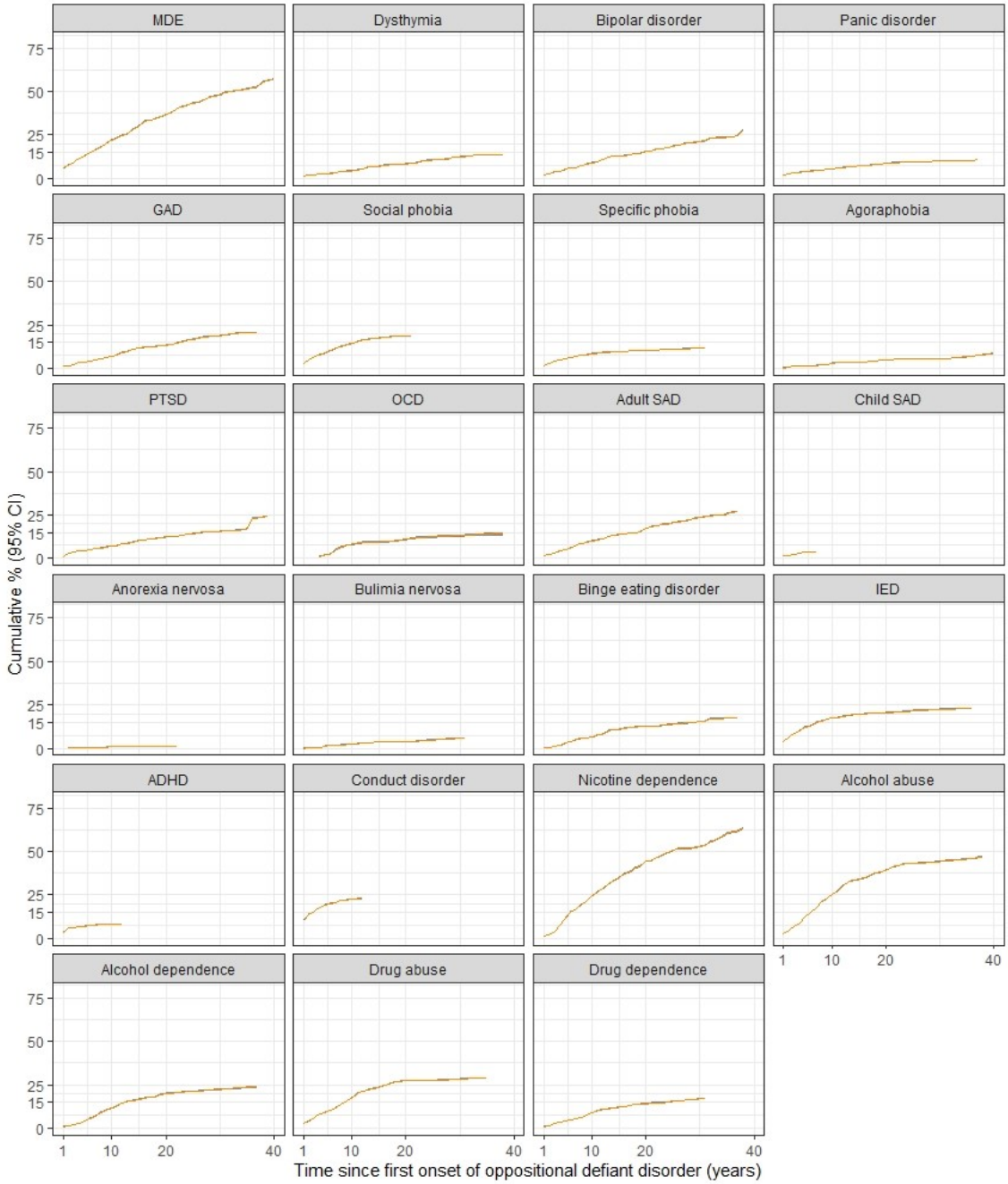


Figure 4t. Absolute risks of later disorders after the initial onset of nicotine dependence

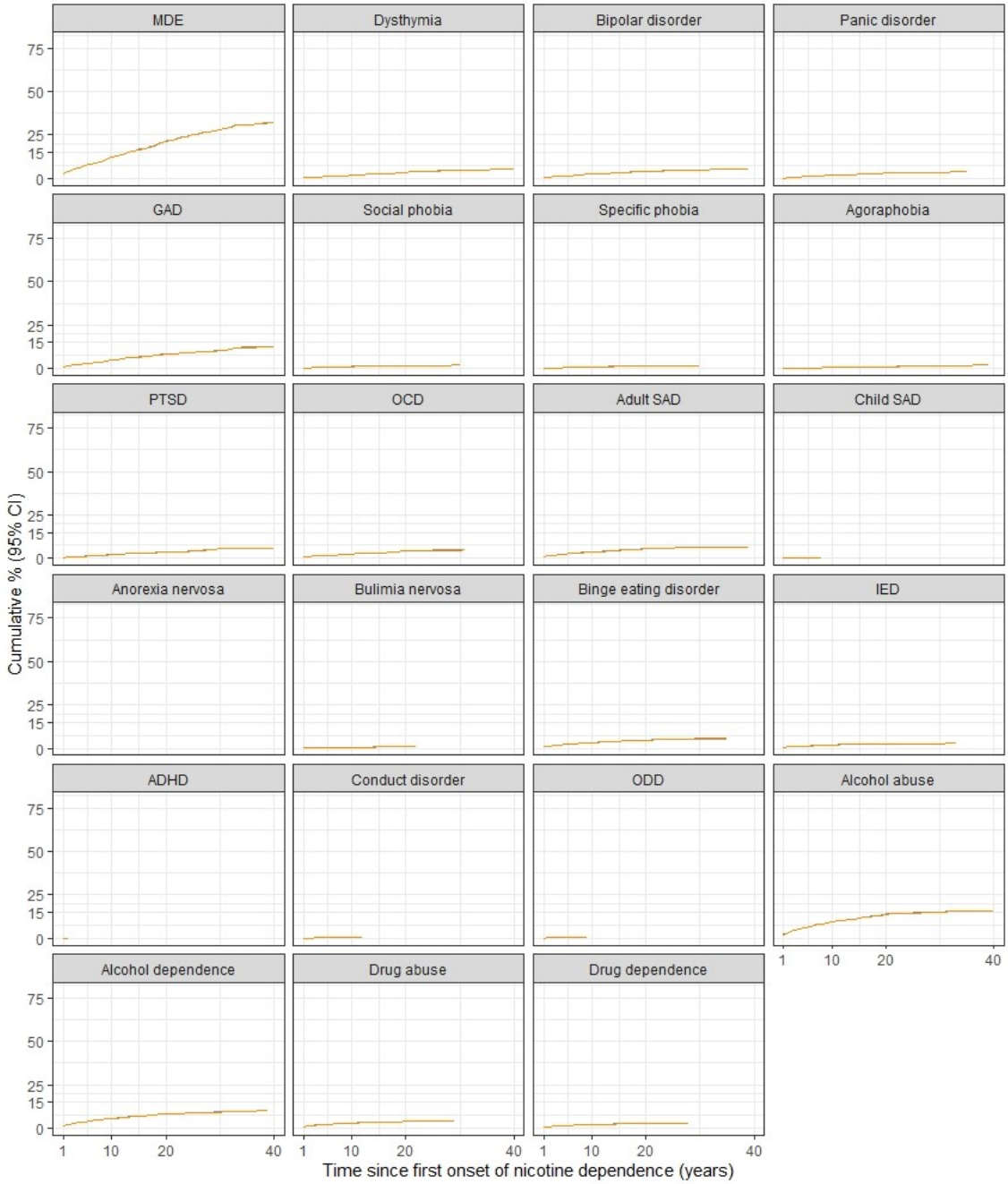


Figure 4u. Absolute risks of later disorders after the initial onset of alcohol abuse

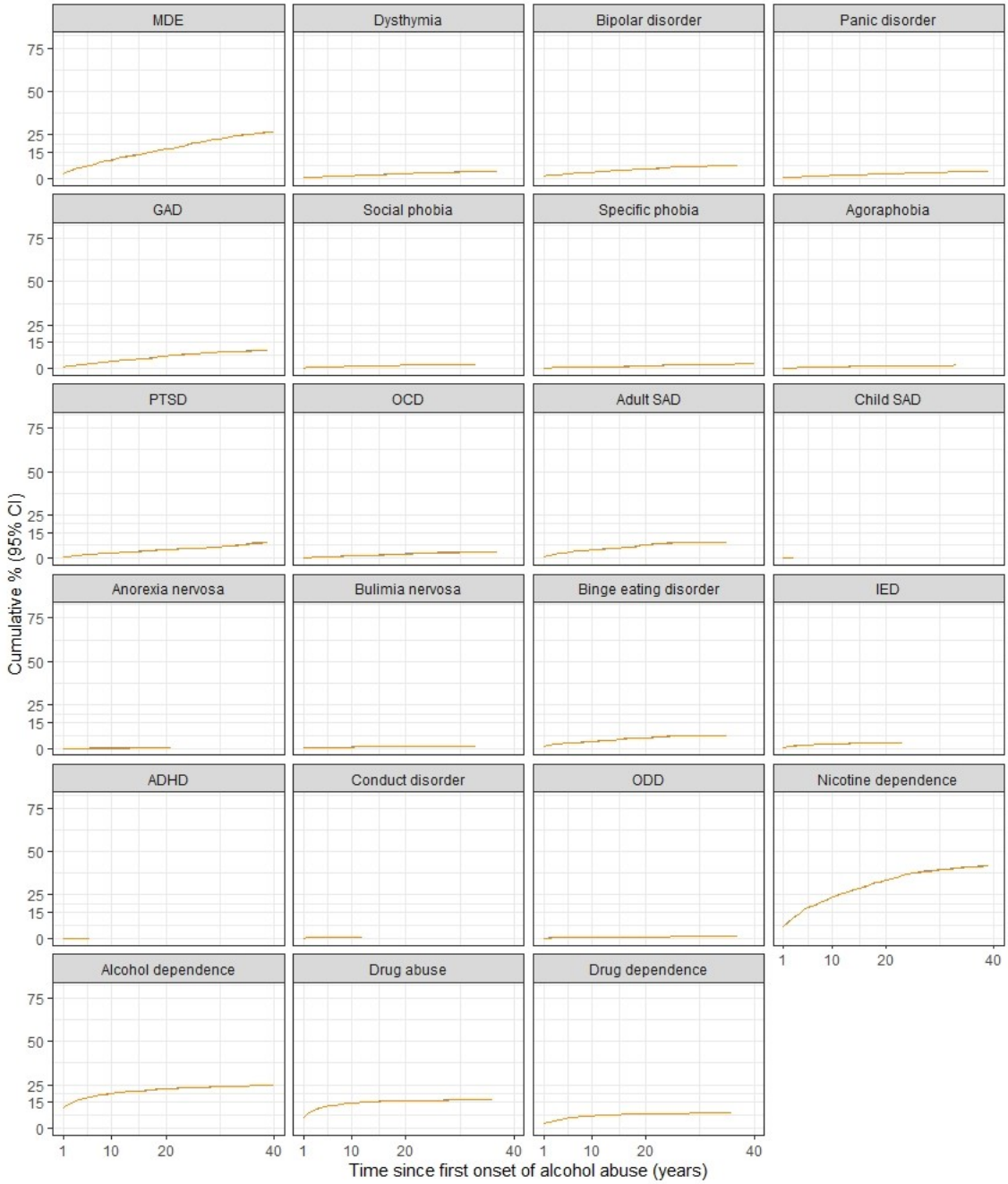


Figure 4v. Absolute risks of later disorders after the initial onset of alcohol dependence

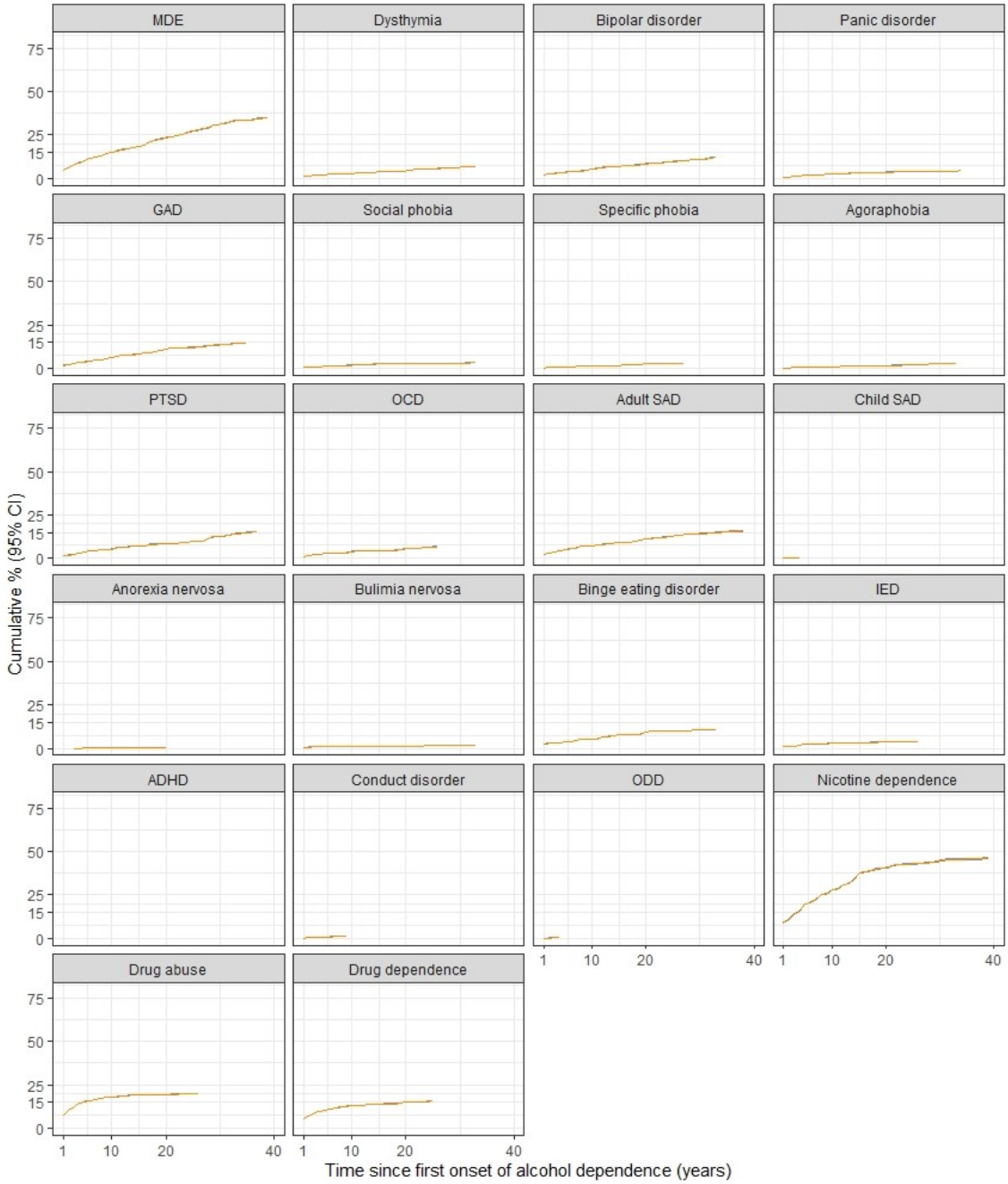


Figure 4w. Absolute risks of later disorders after the initial onset of drug abuse

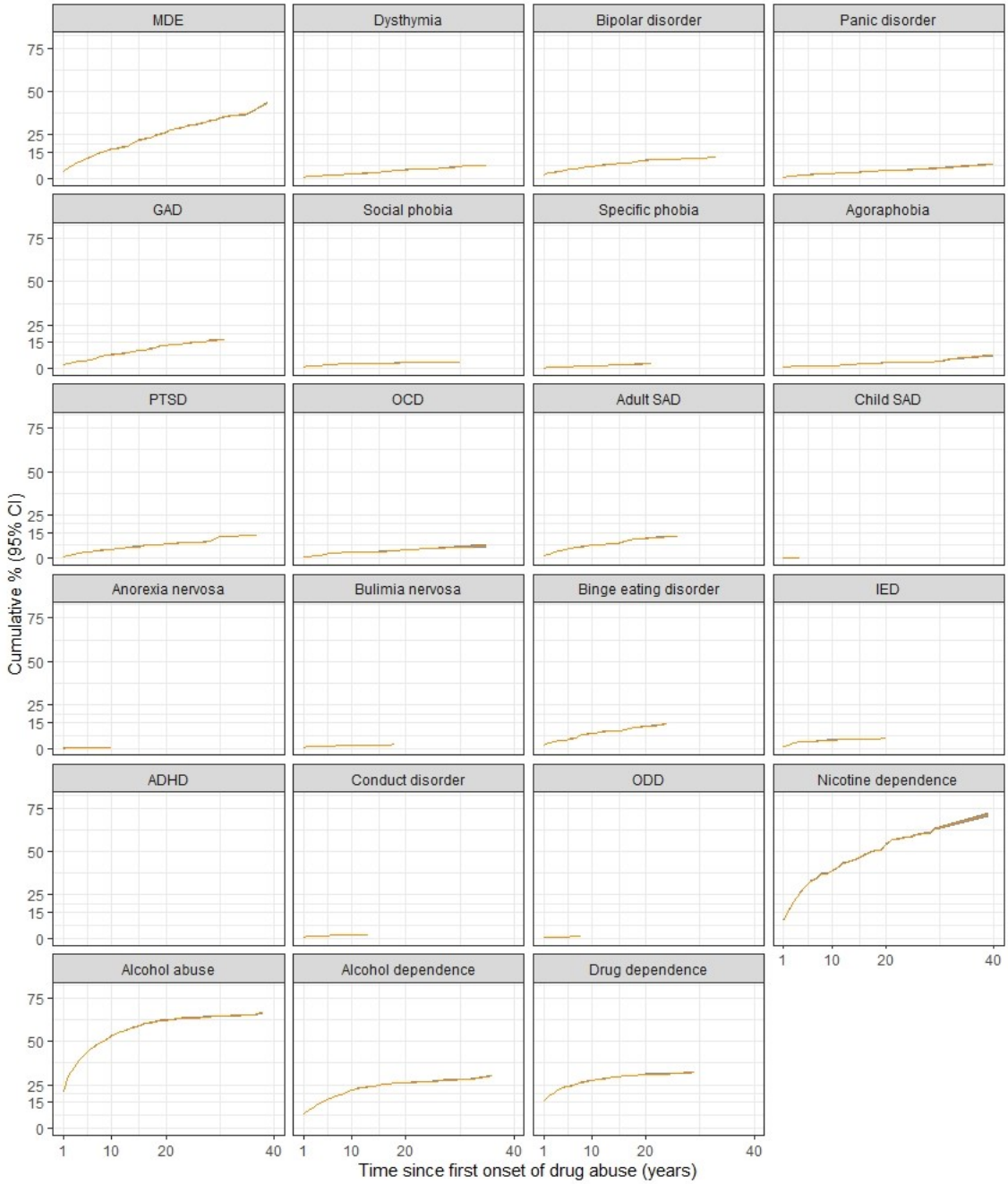
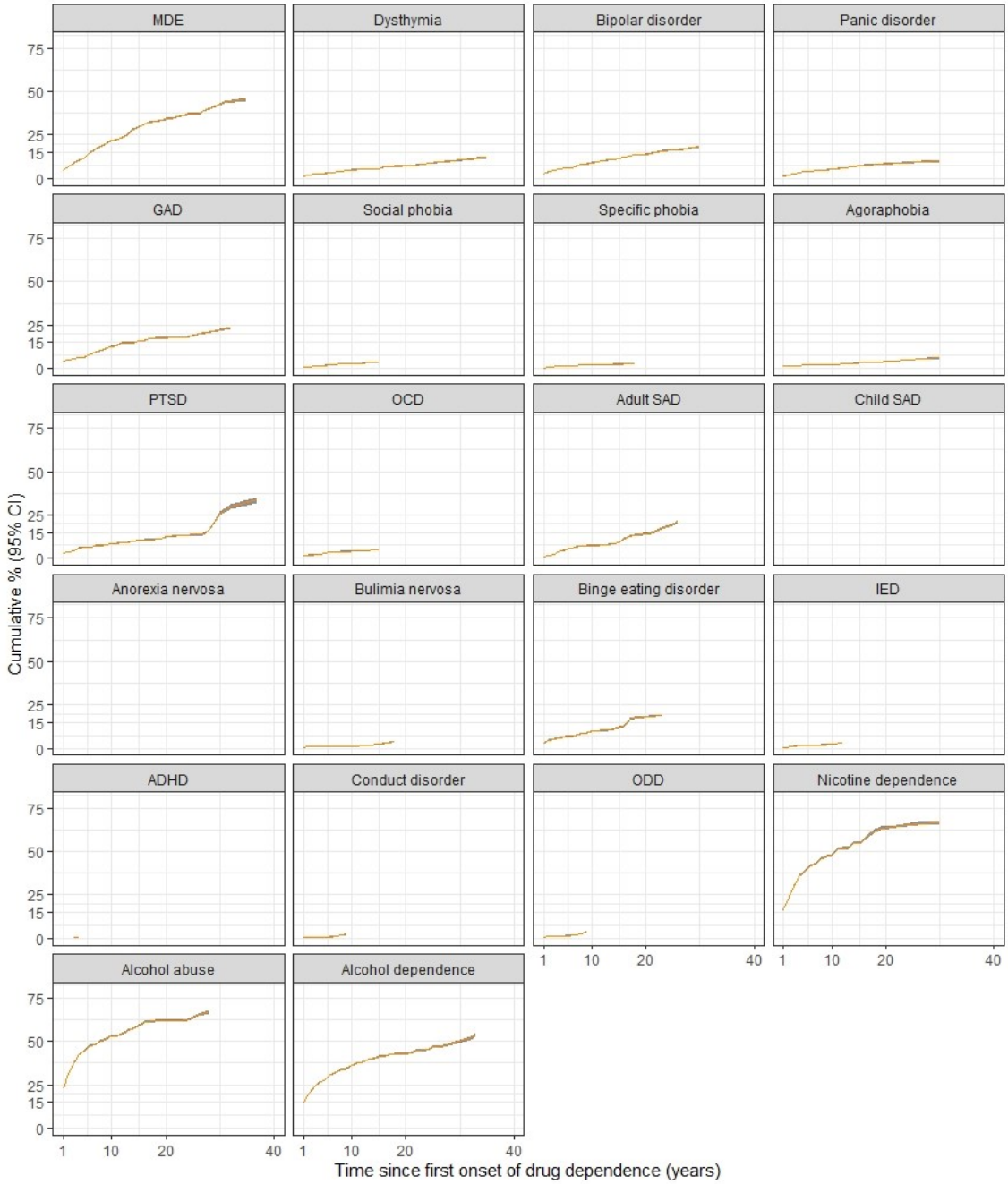


Figure 4x. Absolute risks of later disorders after the initial onset of drug dependence



Supplementary Figure 5. Absolute risks (sex-specific estimate)

Absolute risk of later disorders after the initial onset of a prior disorder (sex specific estimates)

Each panel shows the absolute risks and 95% confidence interval (shaded area) of developing a subsequent later disorder after the onset of prior disorder estimated separately for men (blue line in the plot) and women (pink line in the plot). The label for each later disorder is shown at the top of each panel. The horizontal axis shows the time since onset of prior disorder. The vertical axis shows the cumulative incidence proportions per 100 persons (and 95% CI). Abbreviations: Major Depressive Episode – MDE; Generalized Anxiety Disorder – GAD; Attention Deficit Hyperactivity Disorder (ADHD); Obsessive Compulsive Disorder (OCD); Post-Traumatic Stress Disorder (PTSD); Separation Anxiety Disorder (SAD); Intermittent Explosive Disorder (IED); Oppositional Defiant Disorder (ODD).

Figure 5a. Sex-specific absolute risks of later disorders after the initial onset of major depressive episode (MDE)

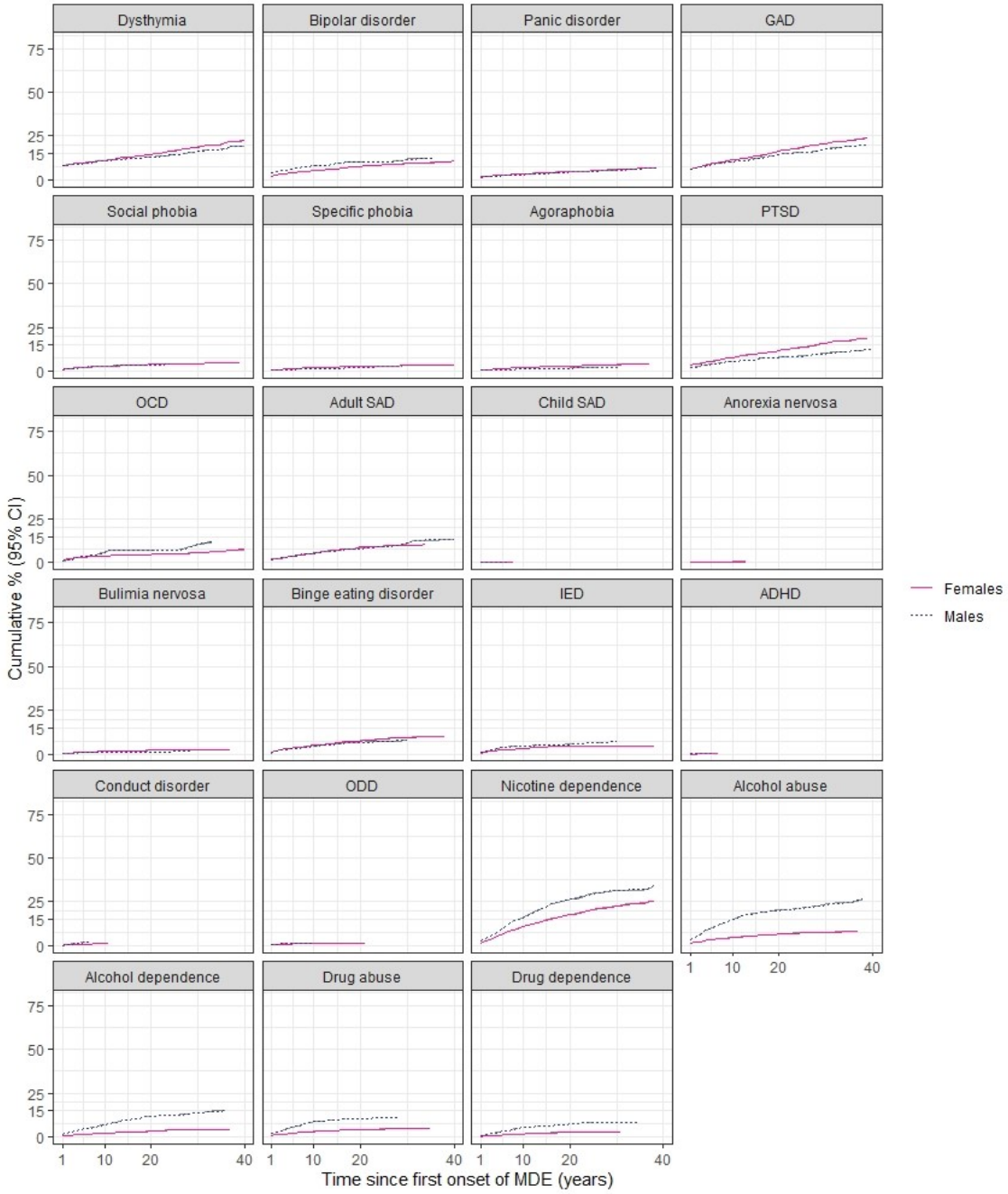


Figure 5b. Sex-specific absolute risks of later disorders after the initial onset of bipolar disorder

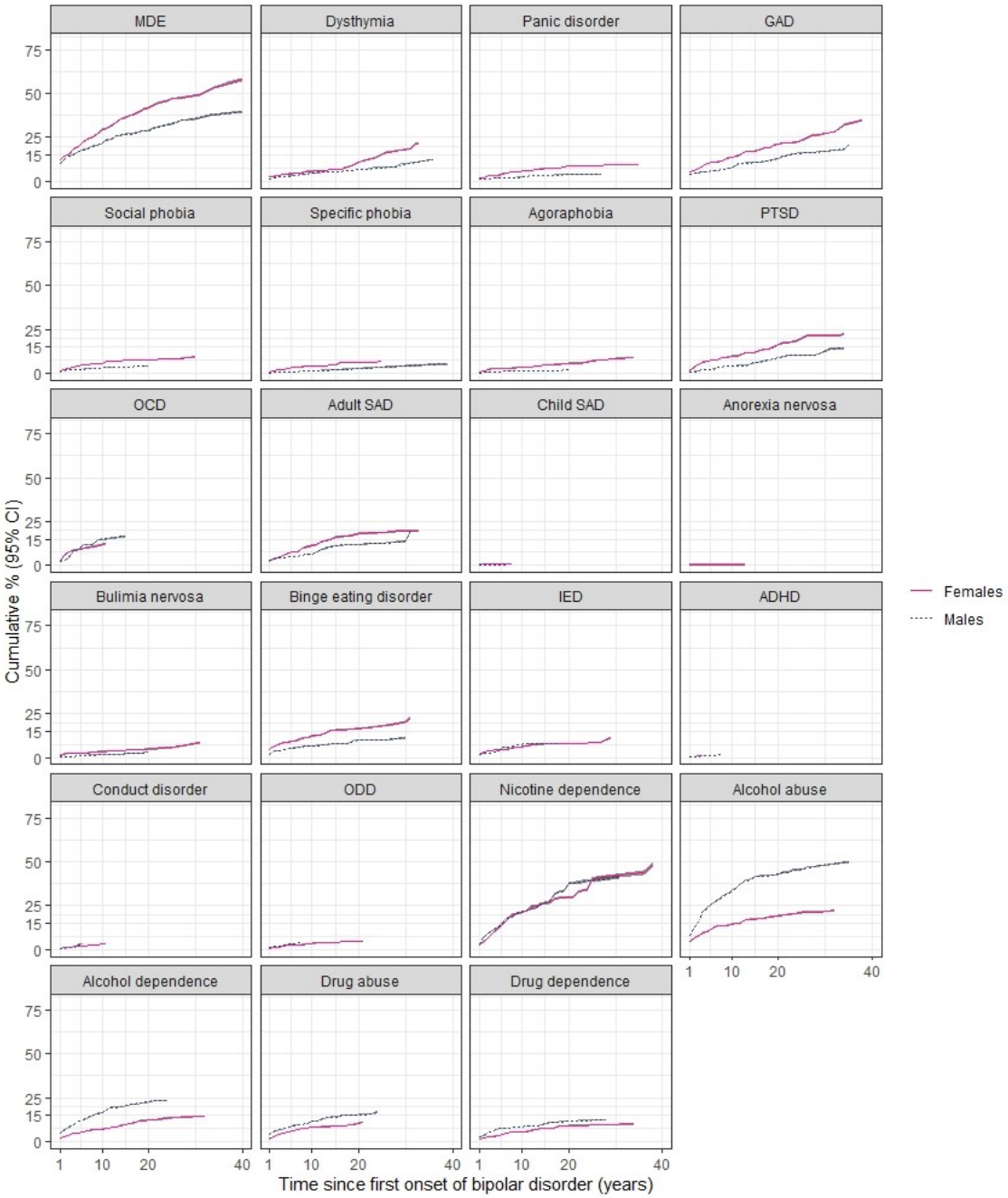


Figure 5c. Sex-specific absolute risks of later disorders after the initial onset of dysthymia

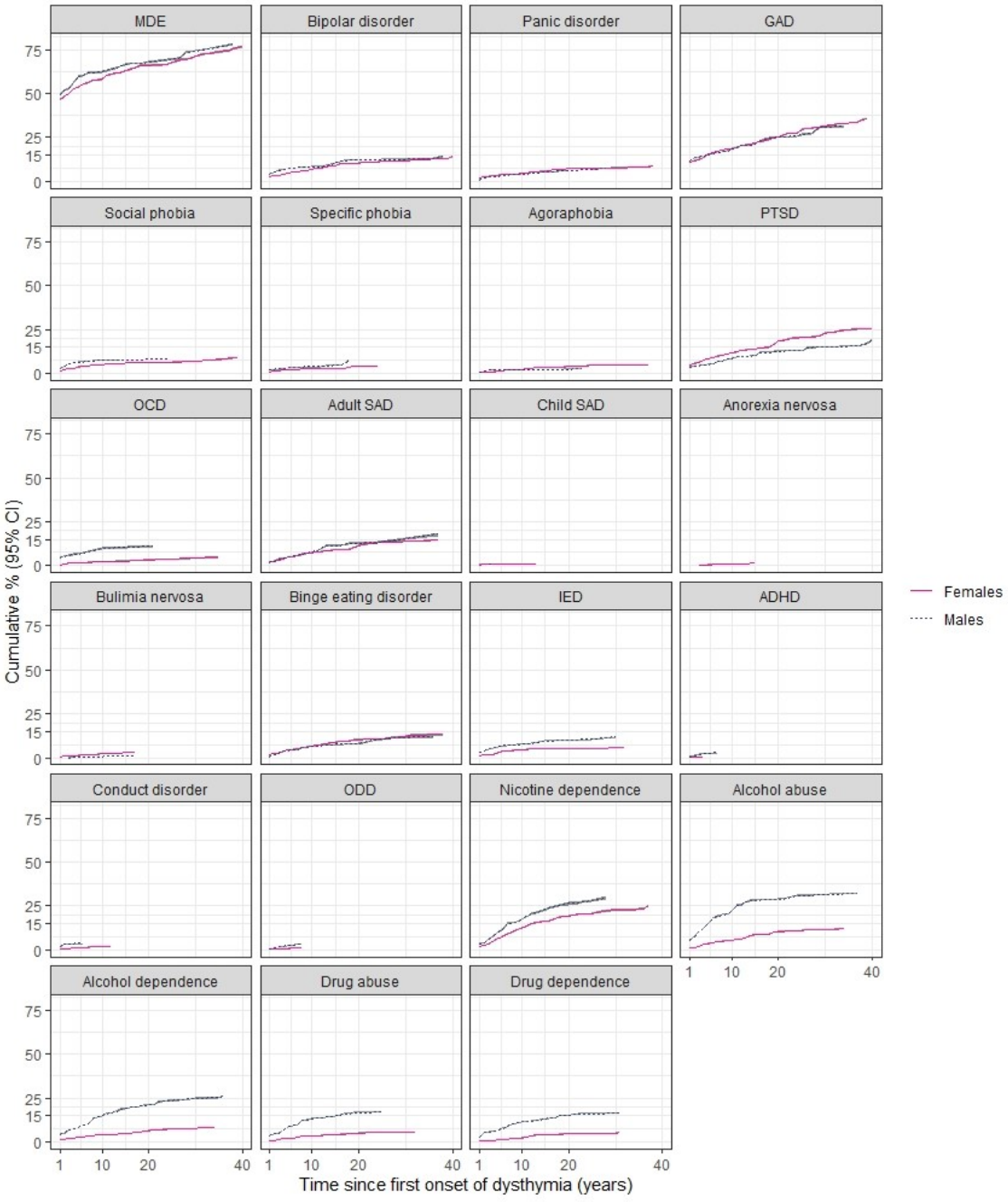


Figure 5d. Sex-specific absolute risks of later disorders after the initial onset of panic disorder

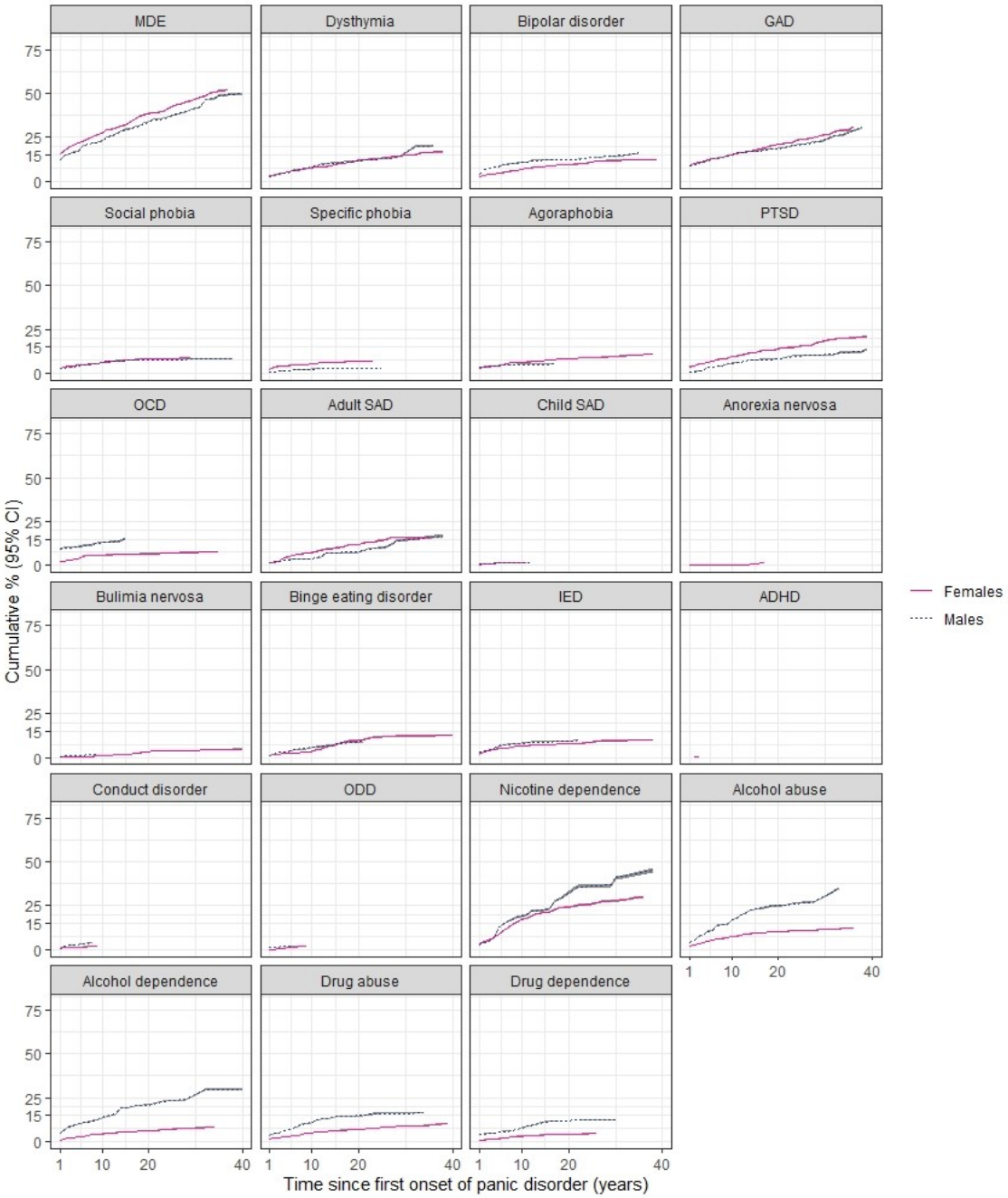


Figure 5e. Sex-specific absolute risks of later disorders after the initial onset of generalized anxiety disorder (GAD)

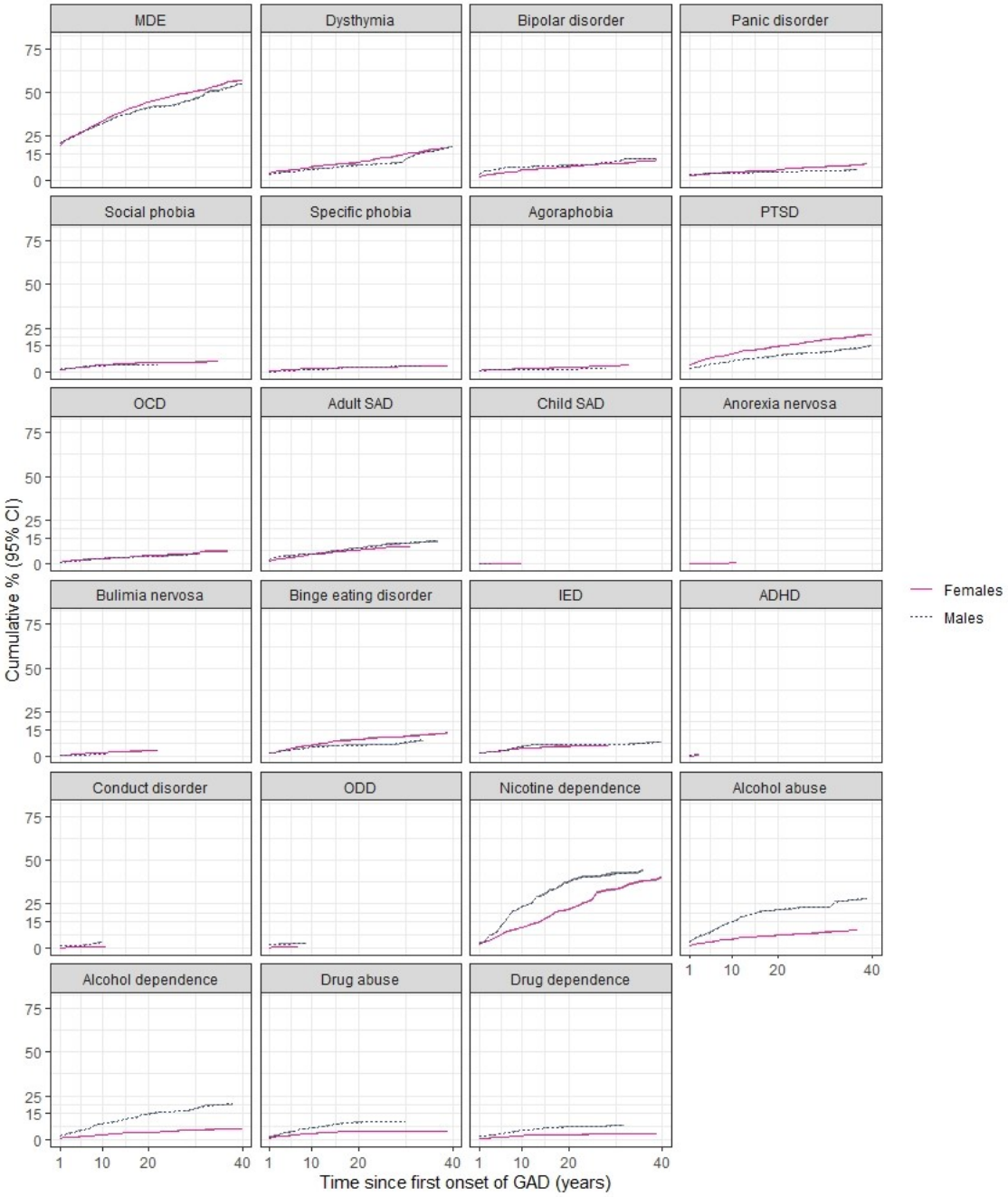


Figure 5f. Sex-specific absolute risks of later disorders after the initial onset of social phobia

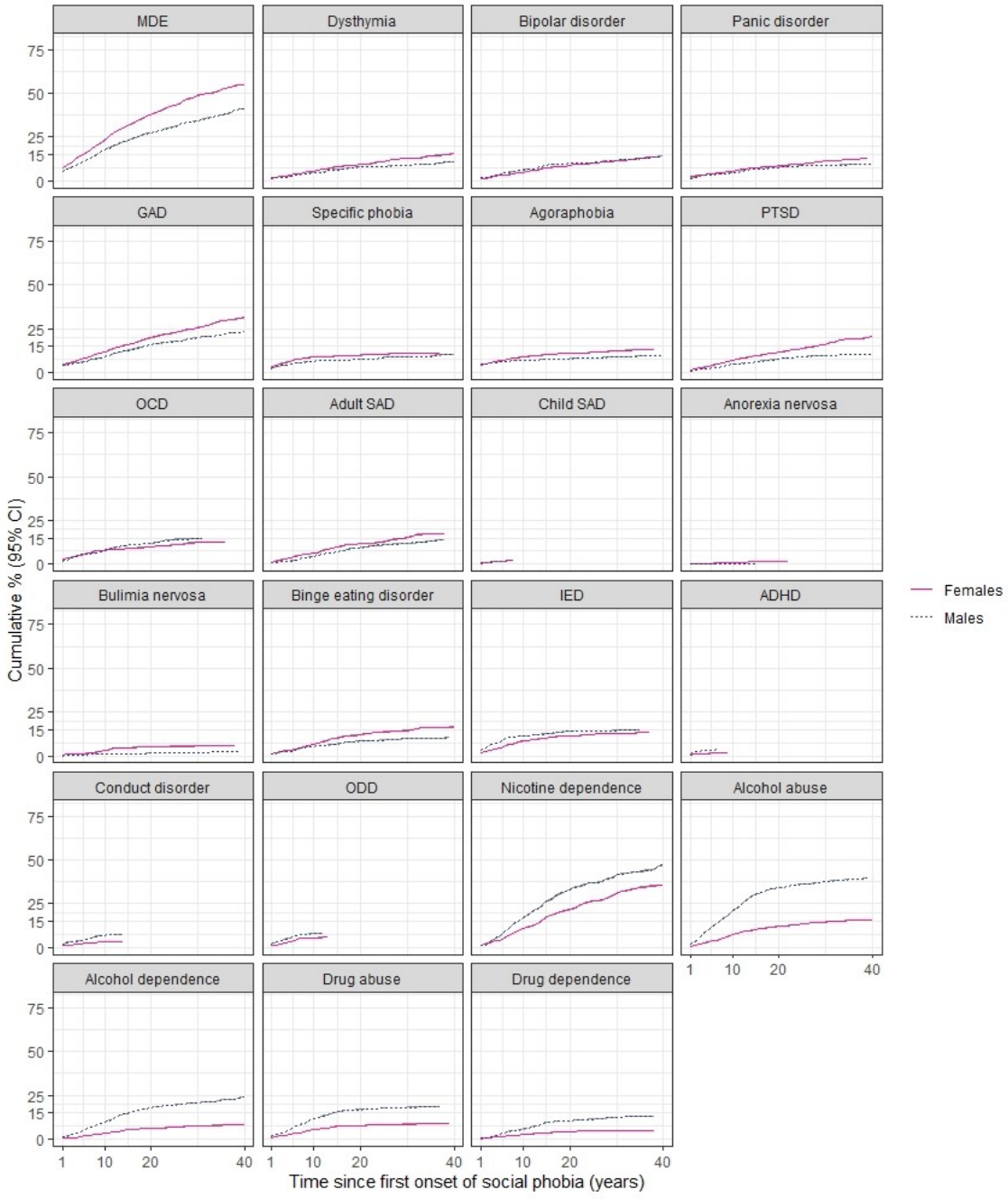


Figure 5g. Sex-specific absolute risks of later disorders after the initial onset of specific phobia

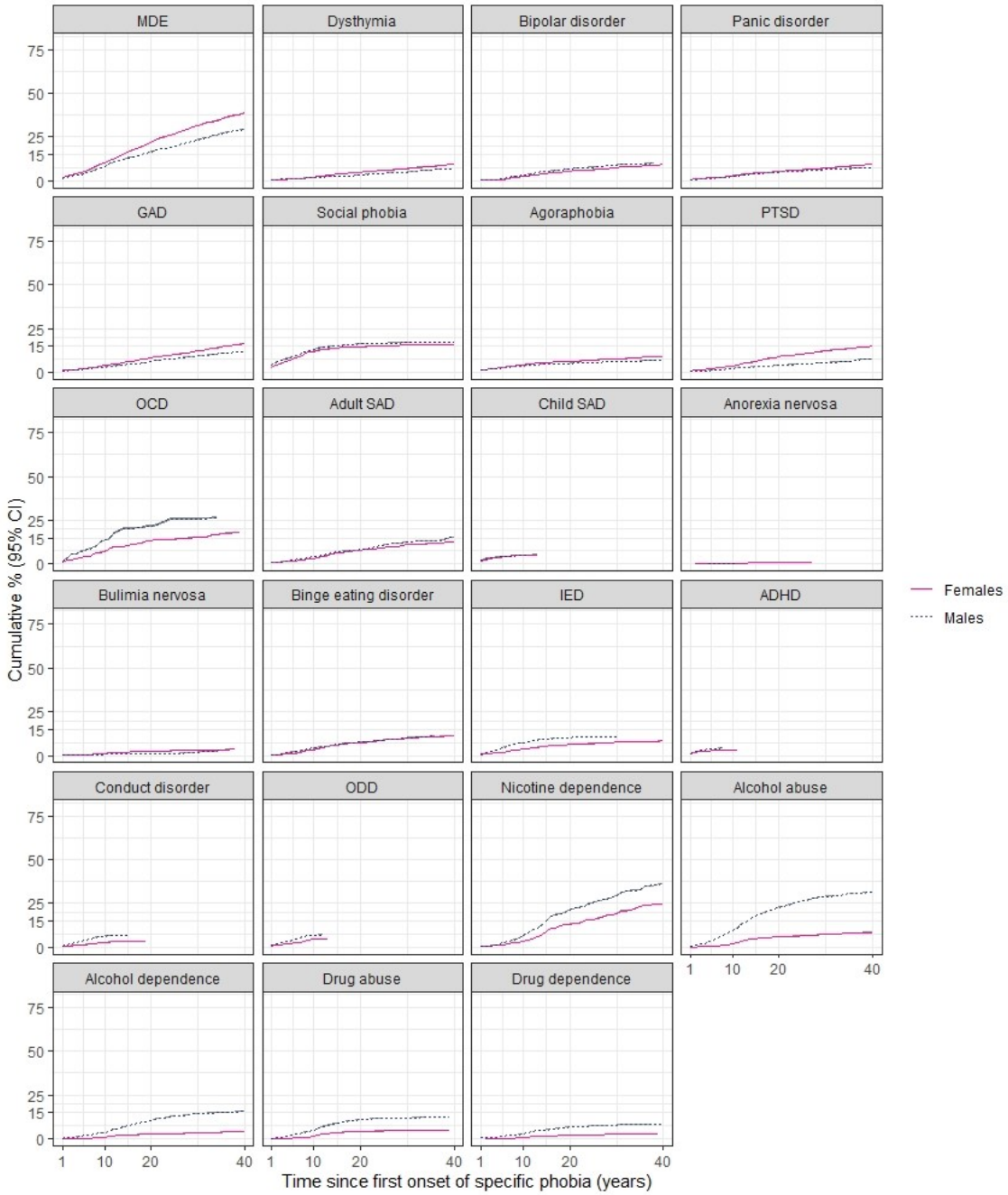


Figure 5h. Sex-specific absolute risks of later disorders after the initial onset of agoraphobia

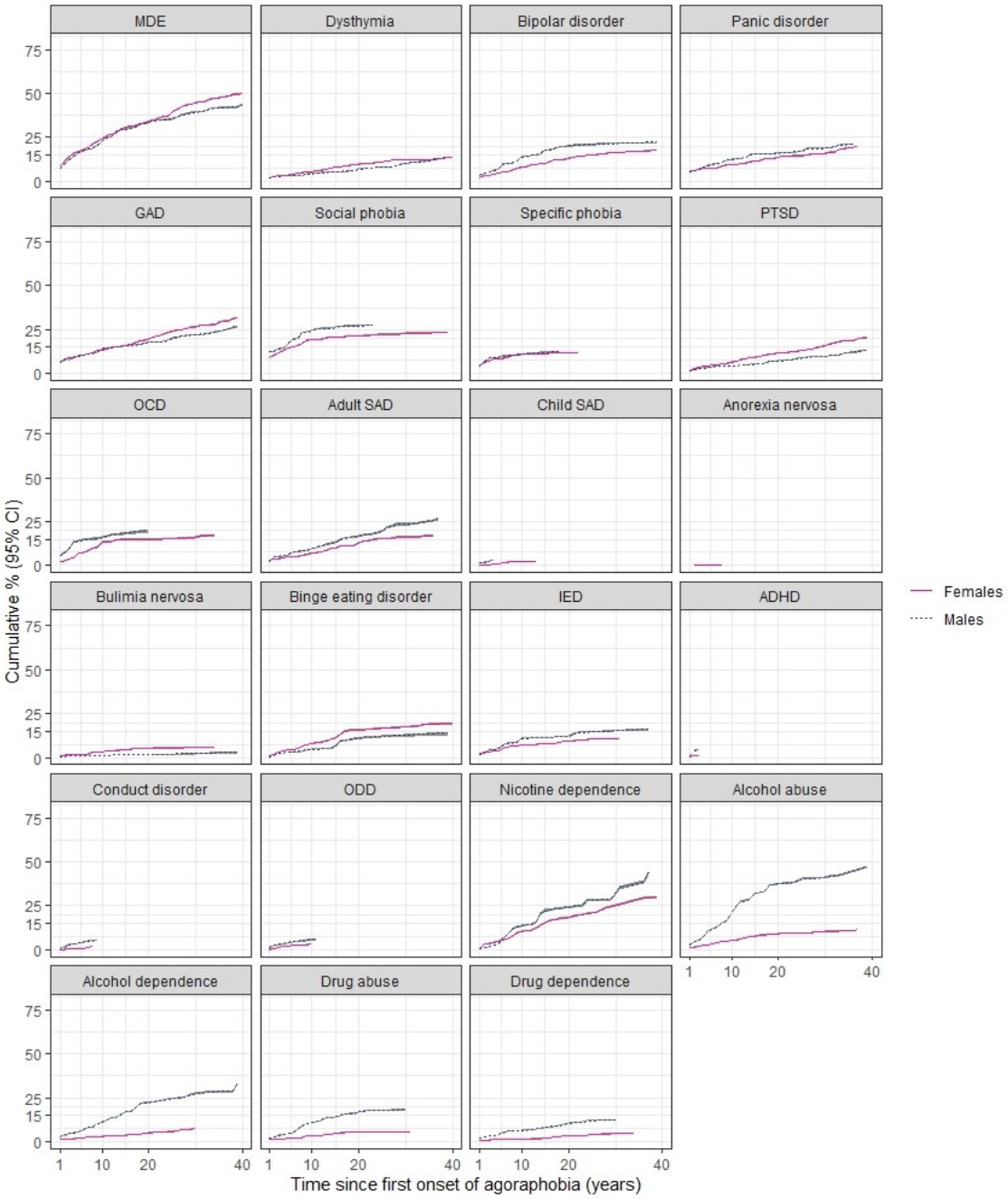


Figure 5i. Sex-specific absolute risks of later disorders after the initial onset of post-traumatic stress disorder (PTSD)

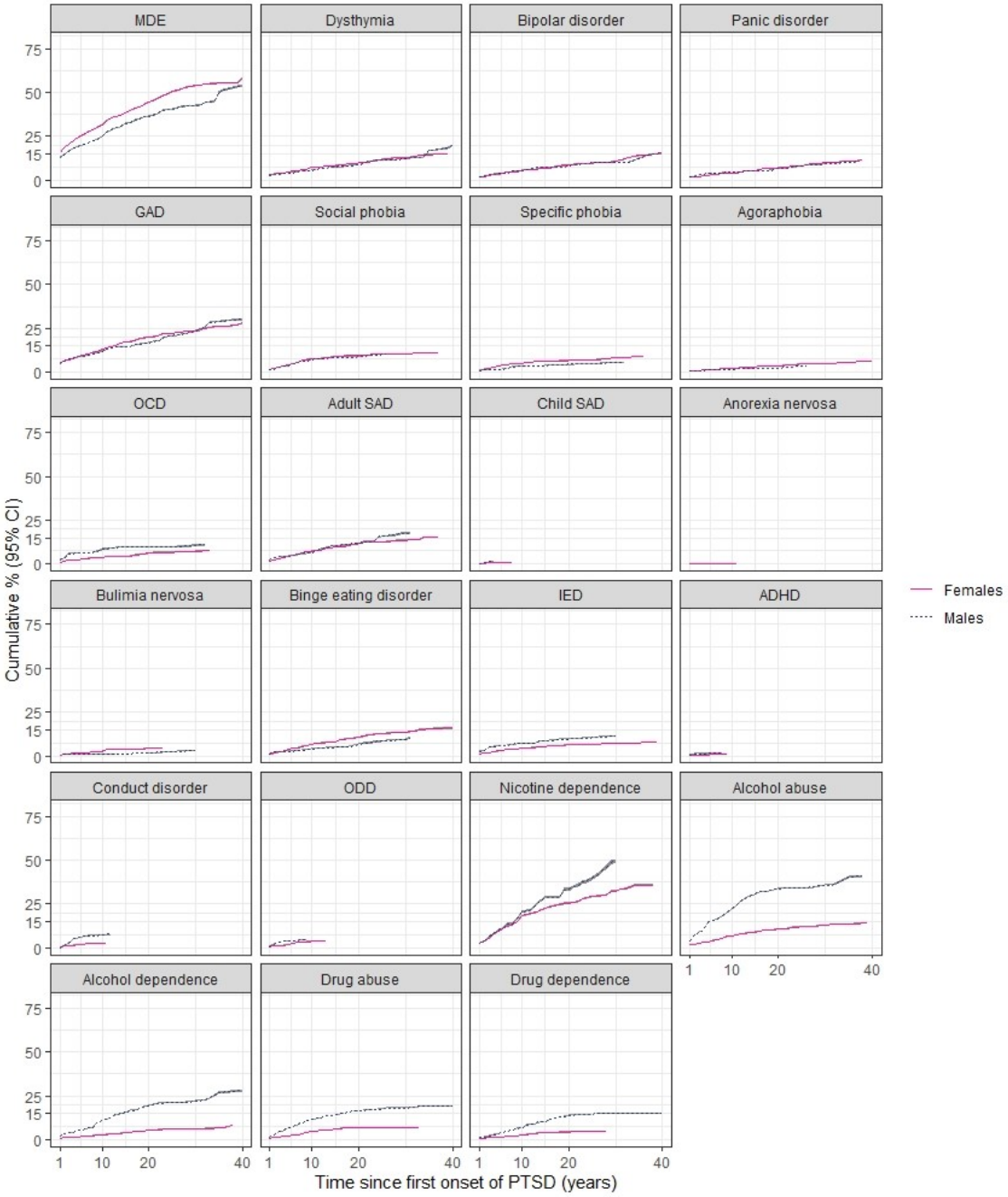


Figure 5j. Sex-specific absolute risks of later disorders after the initial onset of obsessive compulsive disorder (OCD)

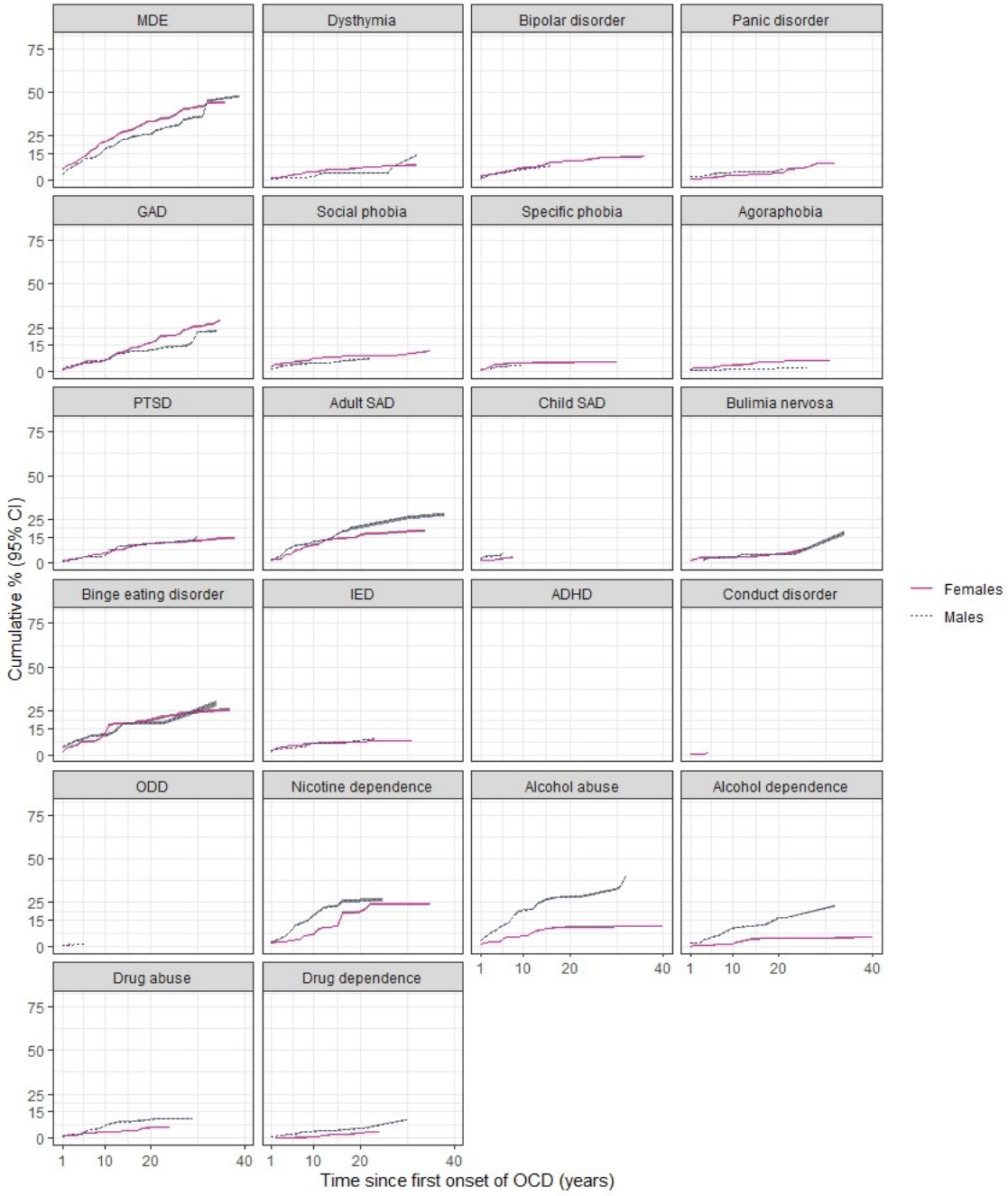


Figure 5k. Sex-specific absolute risks of later disorders after the initial onset of adult separation anxiety disorder

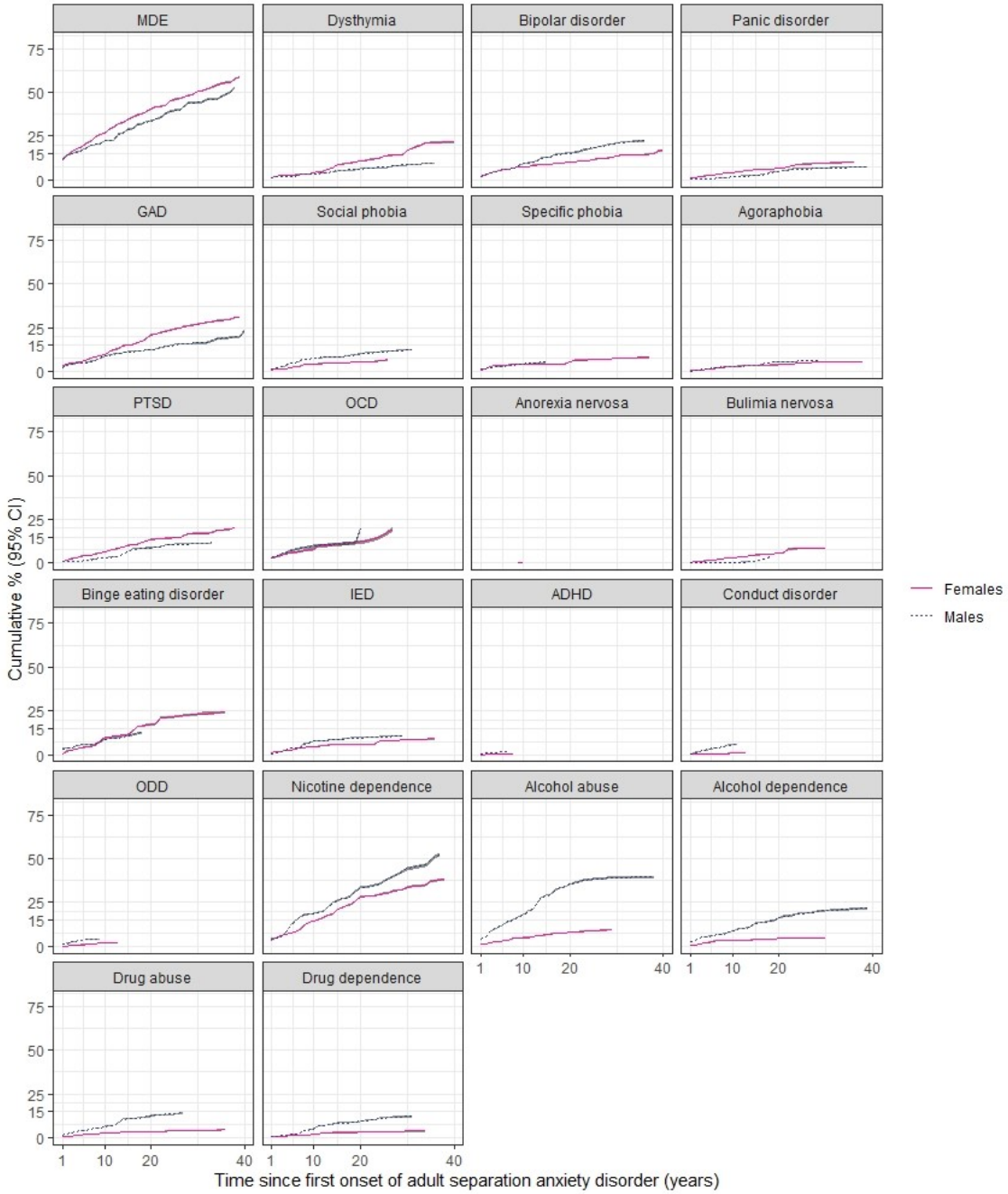


Figure 5l. Sex-specific absolute risks of later disorders after the initial onset of child separation anxiety disorder

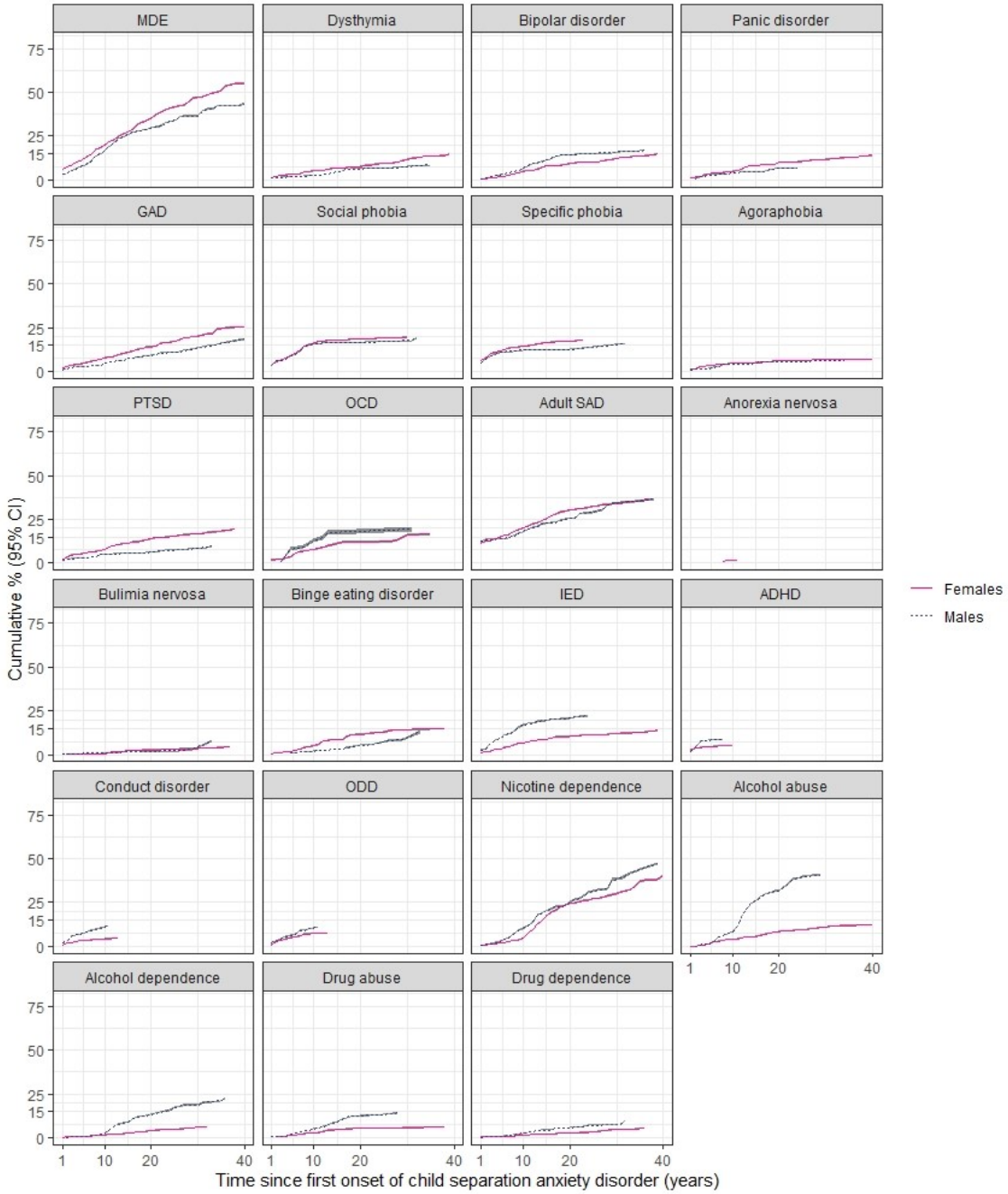


Figure 5m. Sex-specific absolute risks of later disorders after the initial onset of anorexia nervosa

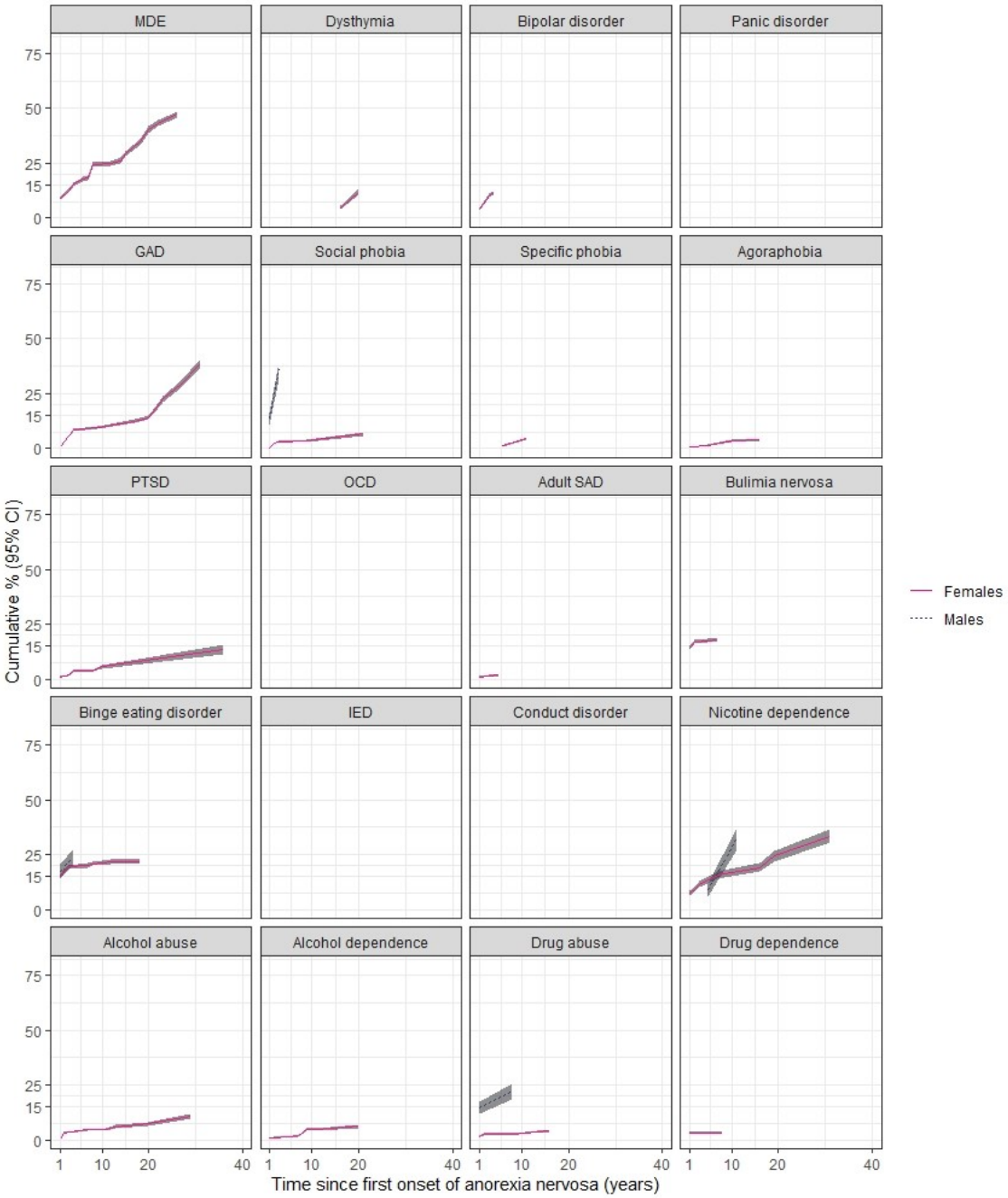


Figure 5n. Sex-specific absolute risks of later disorders after the initial onset of bulimia nervosa

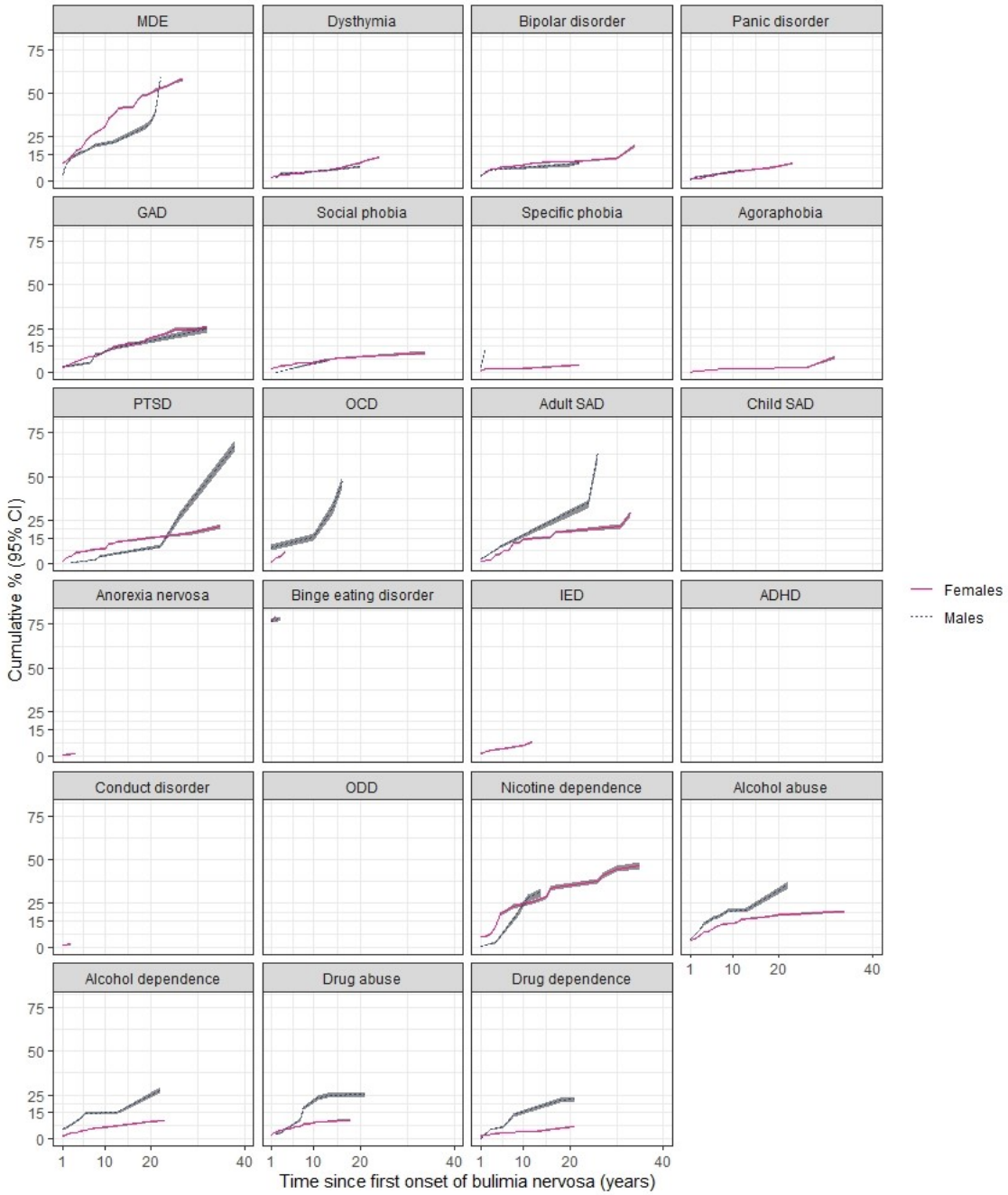


Figure 5o. Sex-specific absolute risks of later disorders after the initial onset of binge eating disorder

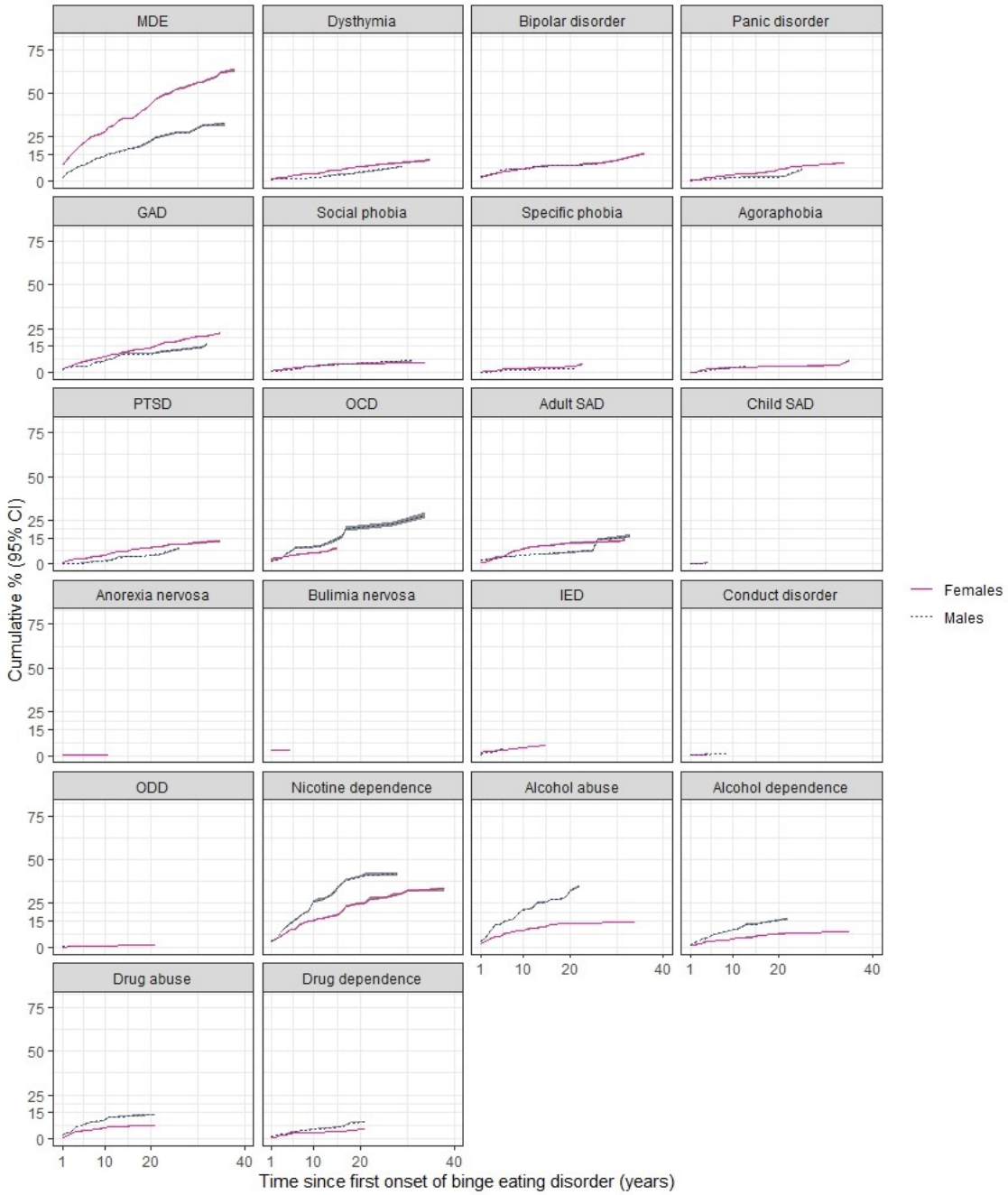


Figure 5p. Sex-specific absolute risks of later disorders after the initial onset of intermittent explosive disorder (IED)

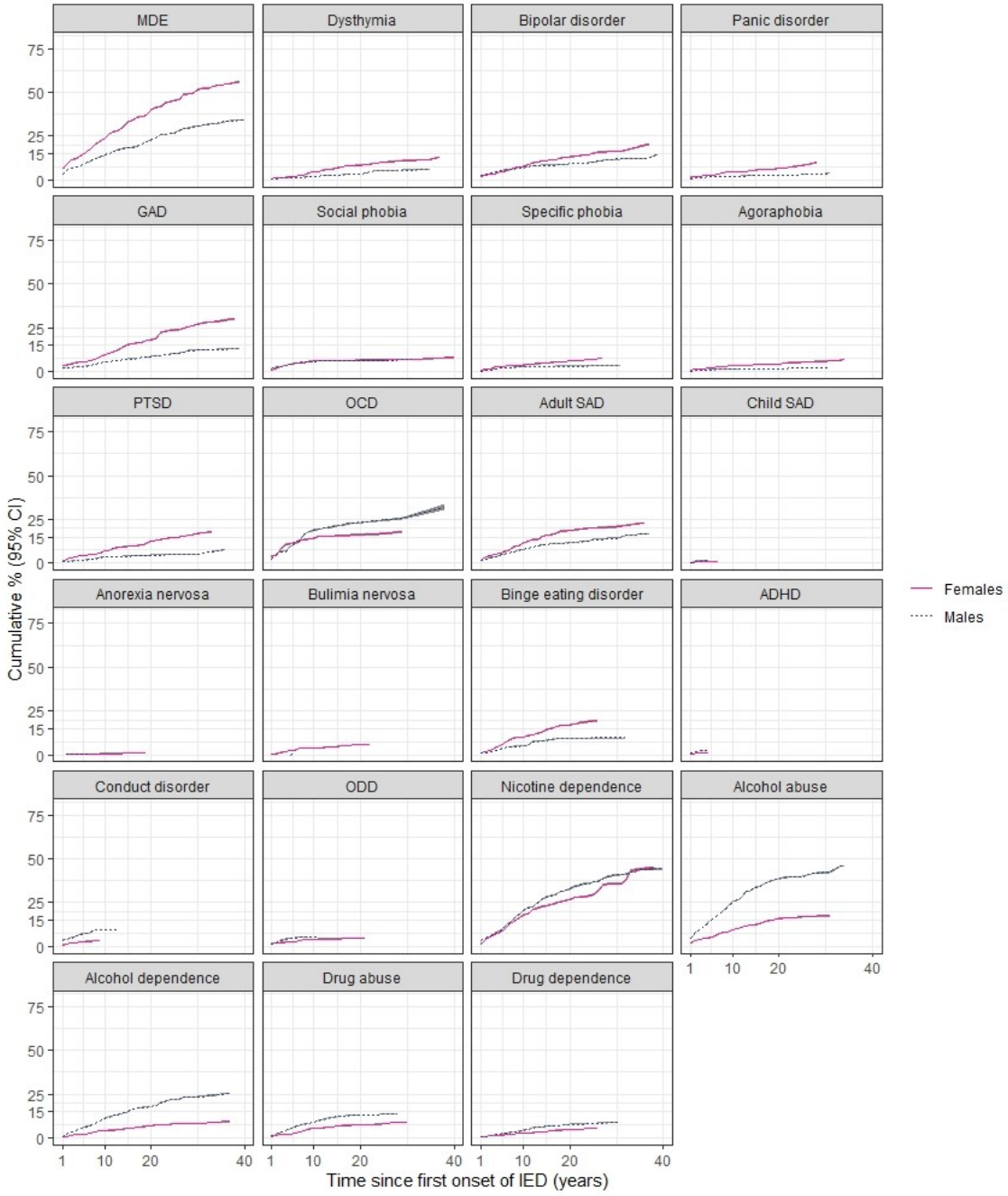


Figure 5q. Sex-specific absolute risks of later disorders after the initial onset of attention deficit hyperactivity disorder (ADHD)

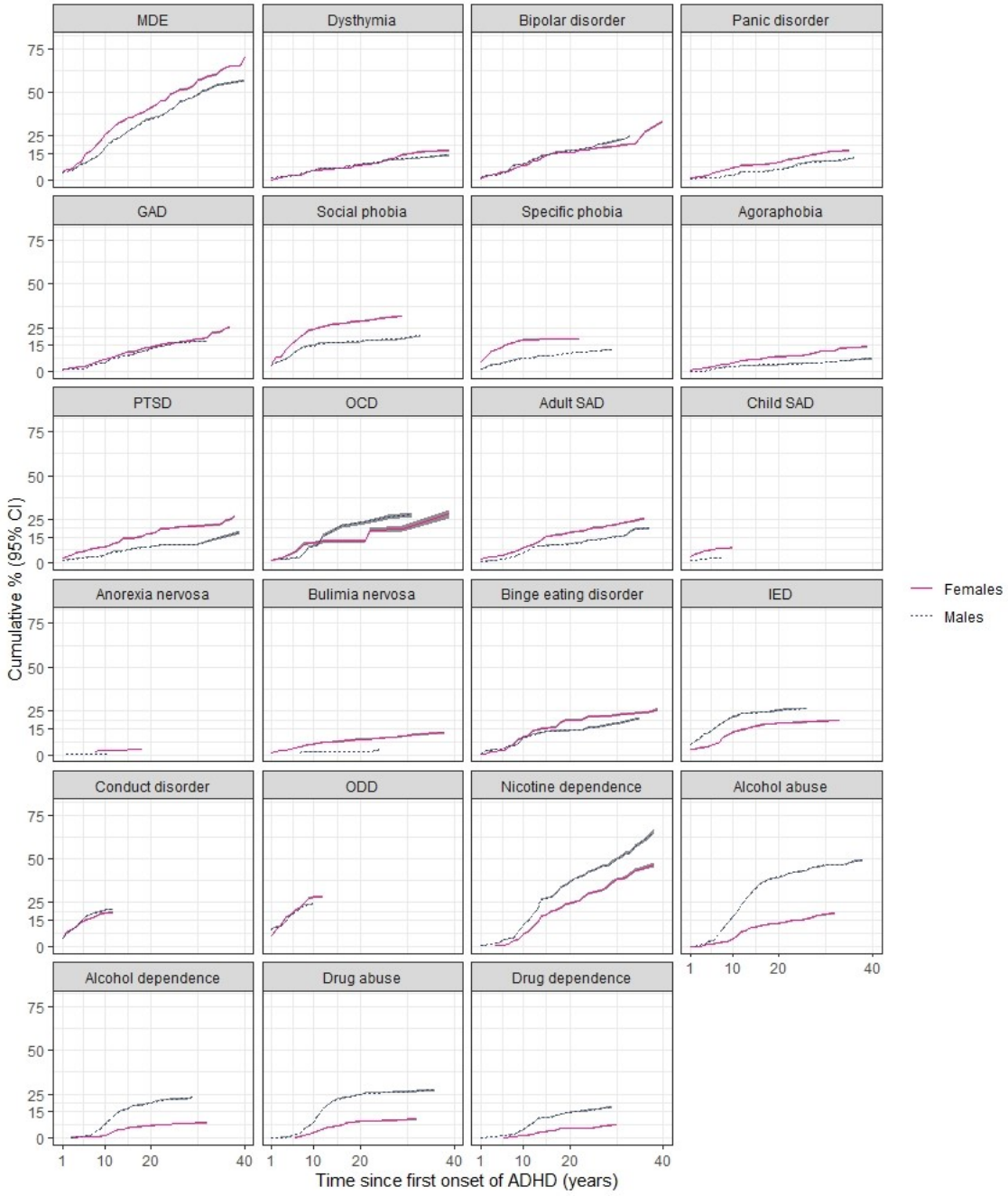


Figure 5r. Sex-specific absolute risks of later disorders after the initial onset of conduct disorder

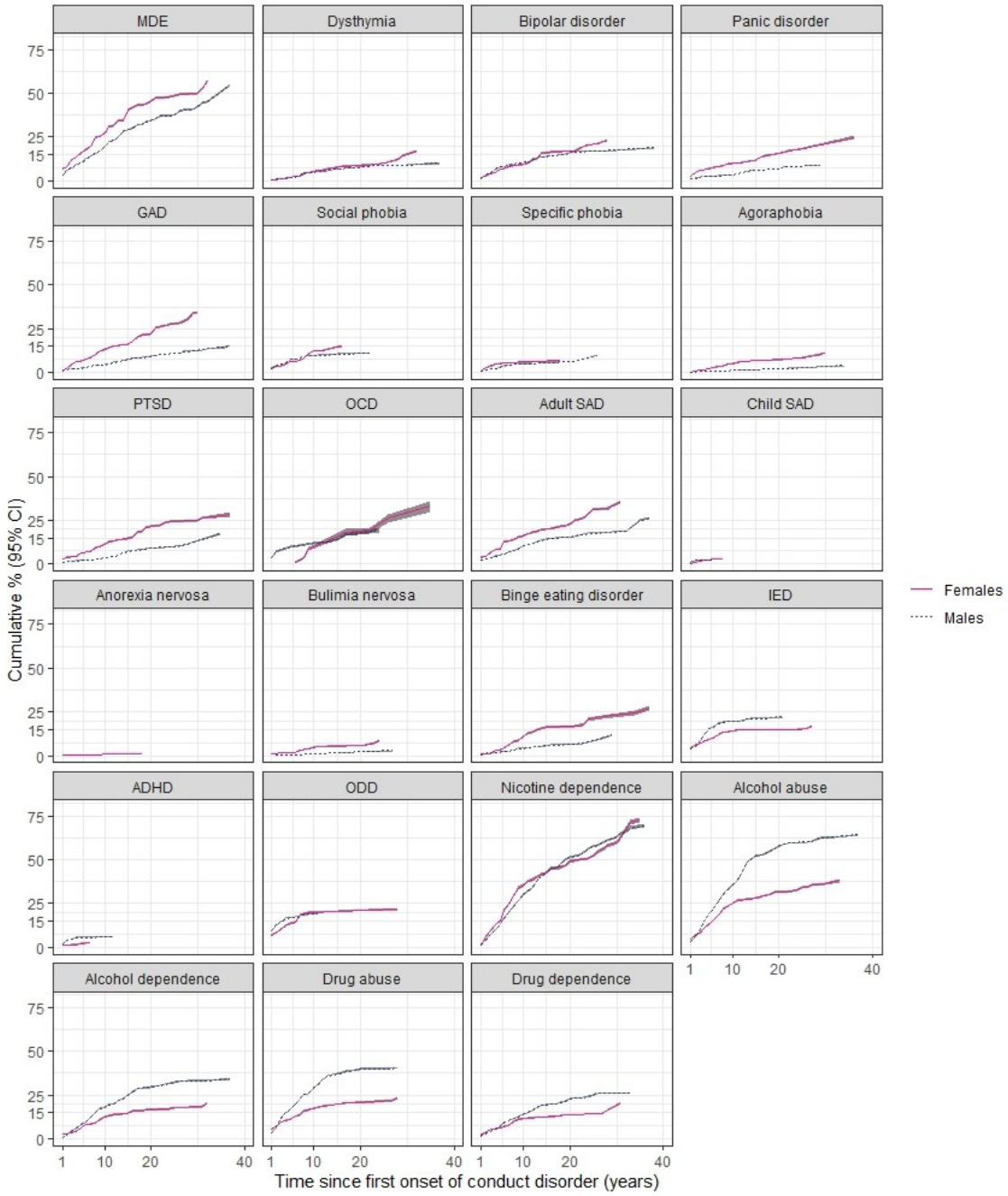


Figure 5s. Sex-specific absolute risks of later disorders after the initial onset of oppositional defiant disorder (ODD)

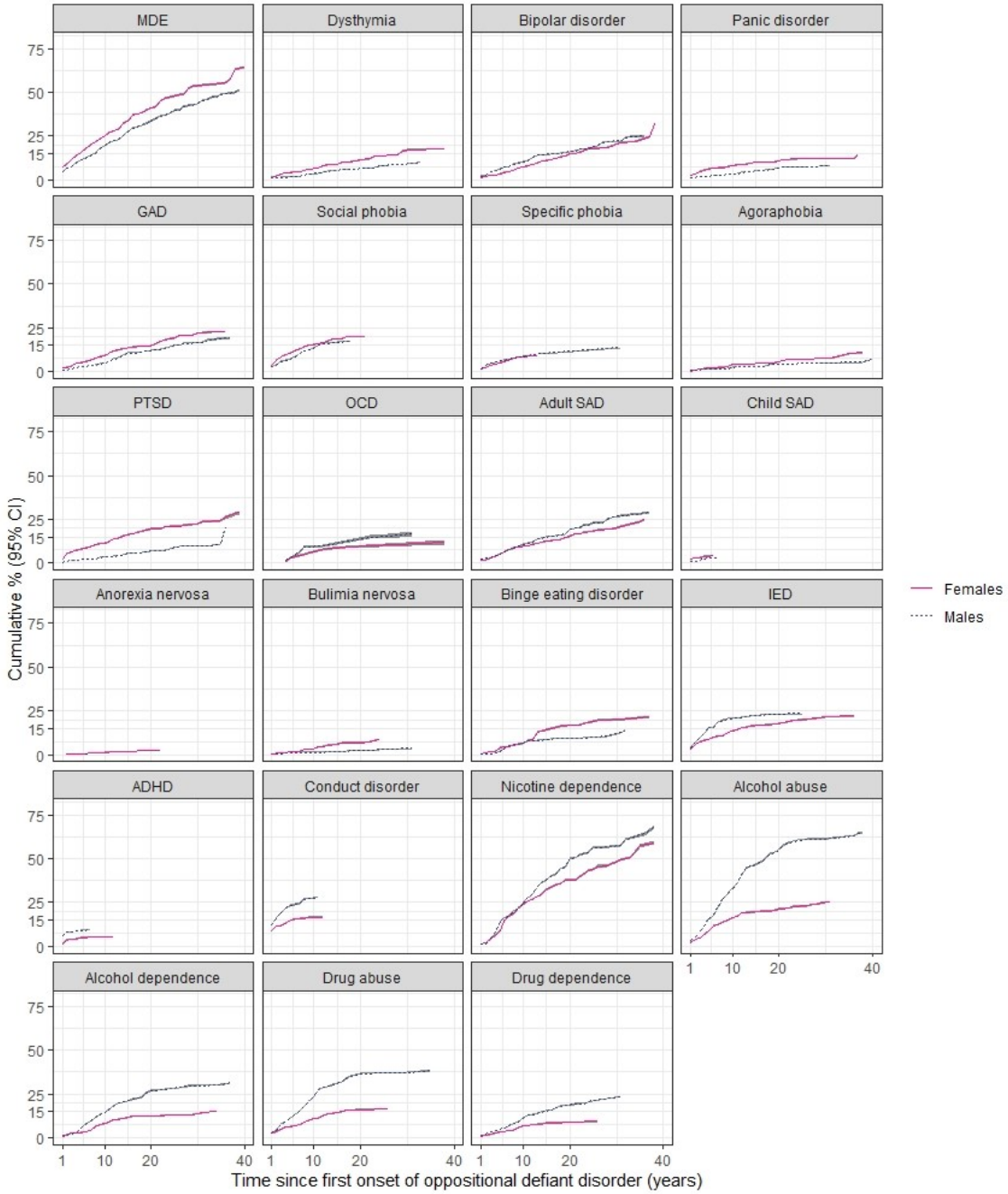


Figure 5t. Sex-specific absolute risks of later disorders after the initial onset of nicotine dependence

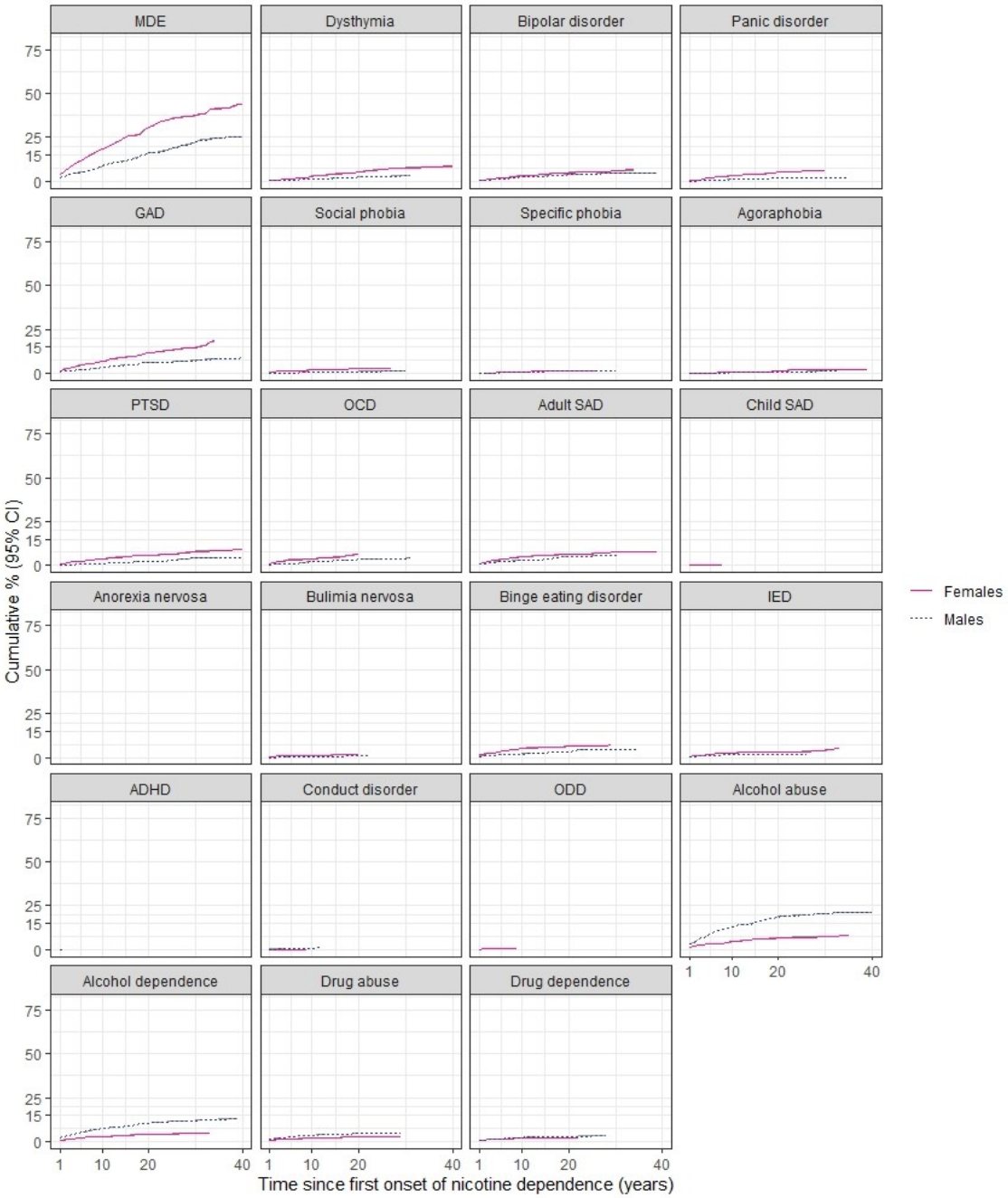


Figure 5u. Sex-specific absolute risks of later disorders after the initial onset of alcohol abuse

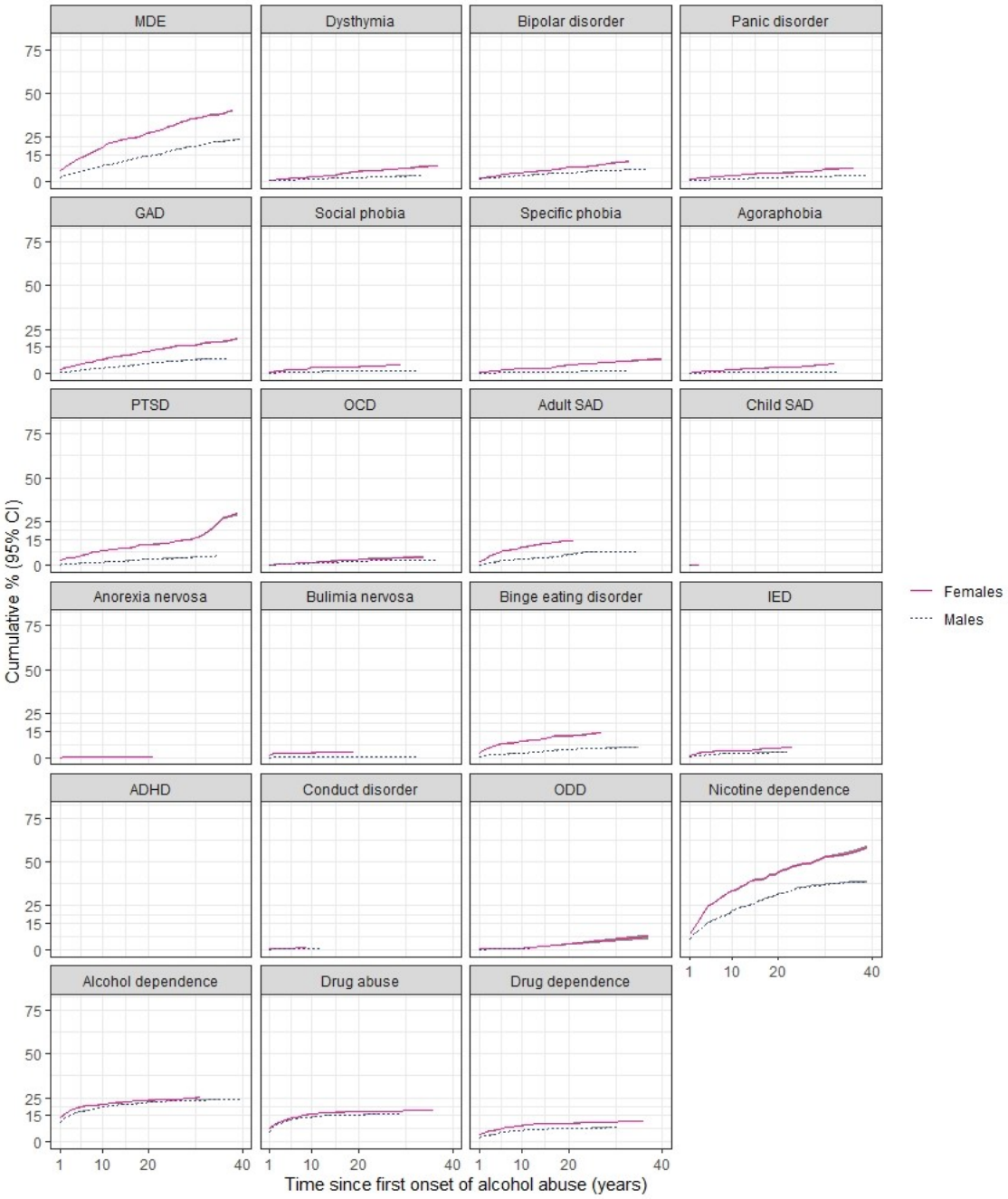


Figure 5v. Sex-specific absolute risks of later disorders after the initial onset of alcohol dependence

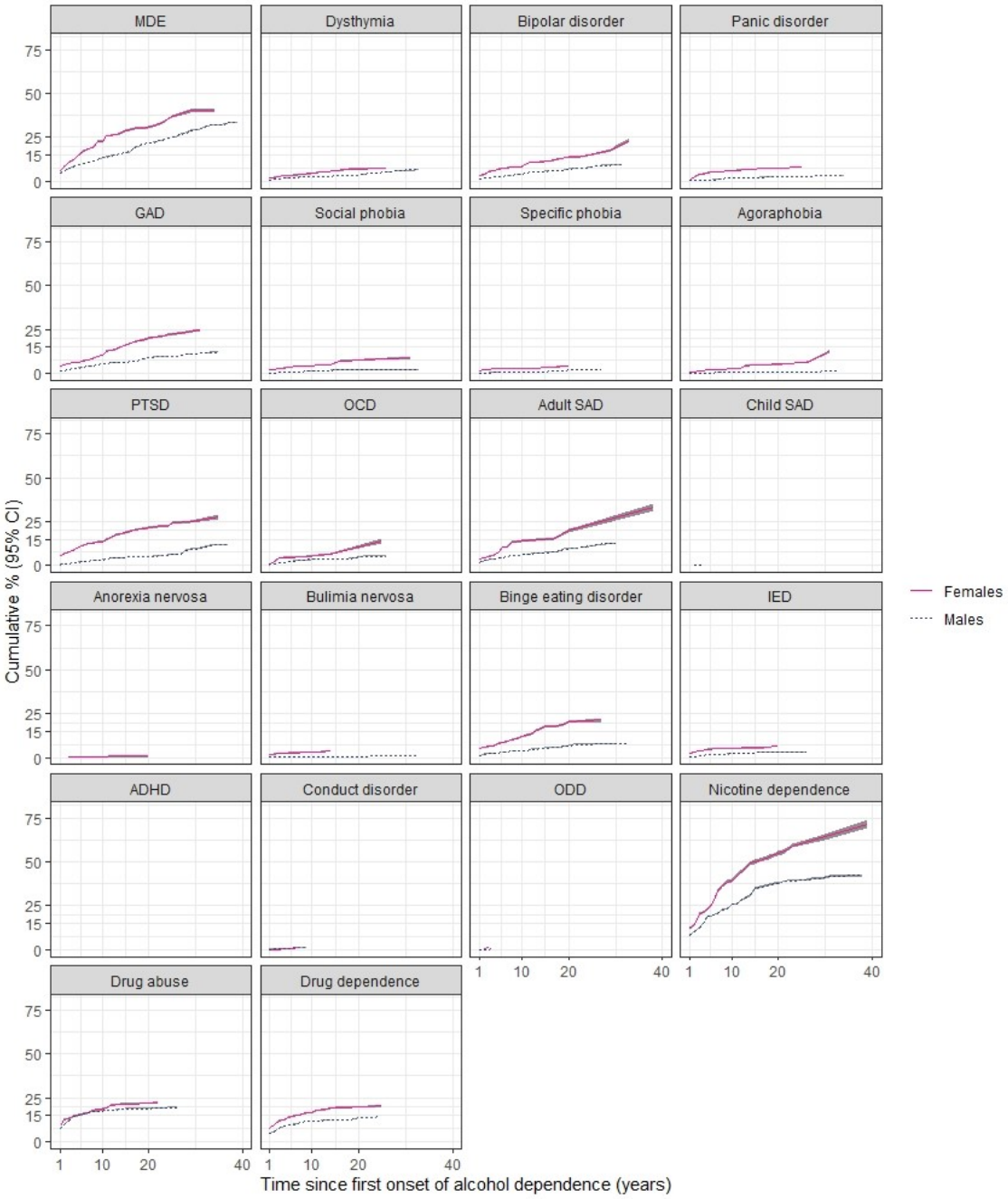


Figure 5w. Sex-specific absolute risks of later disorders after the initial onset of drug abuse

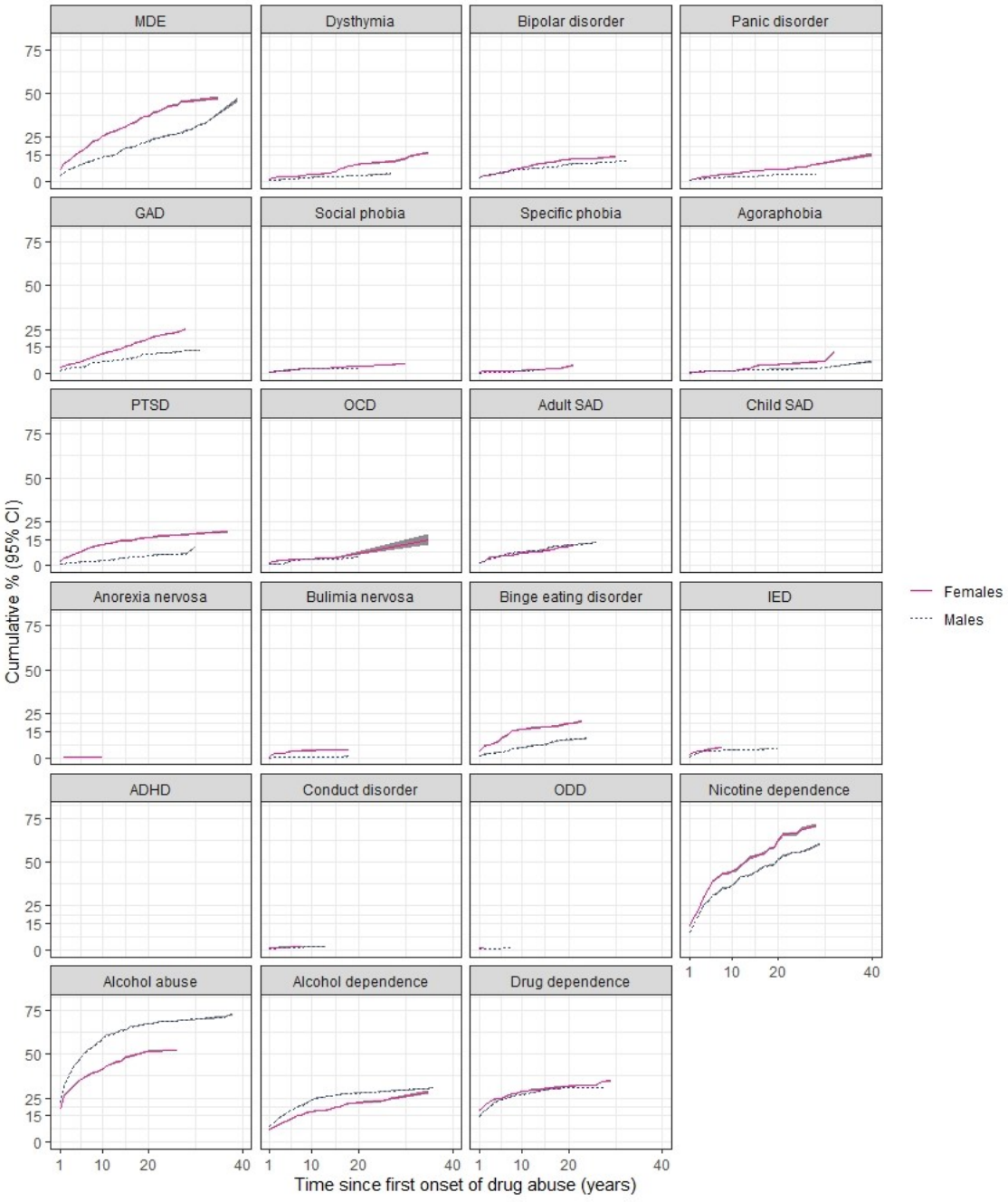
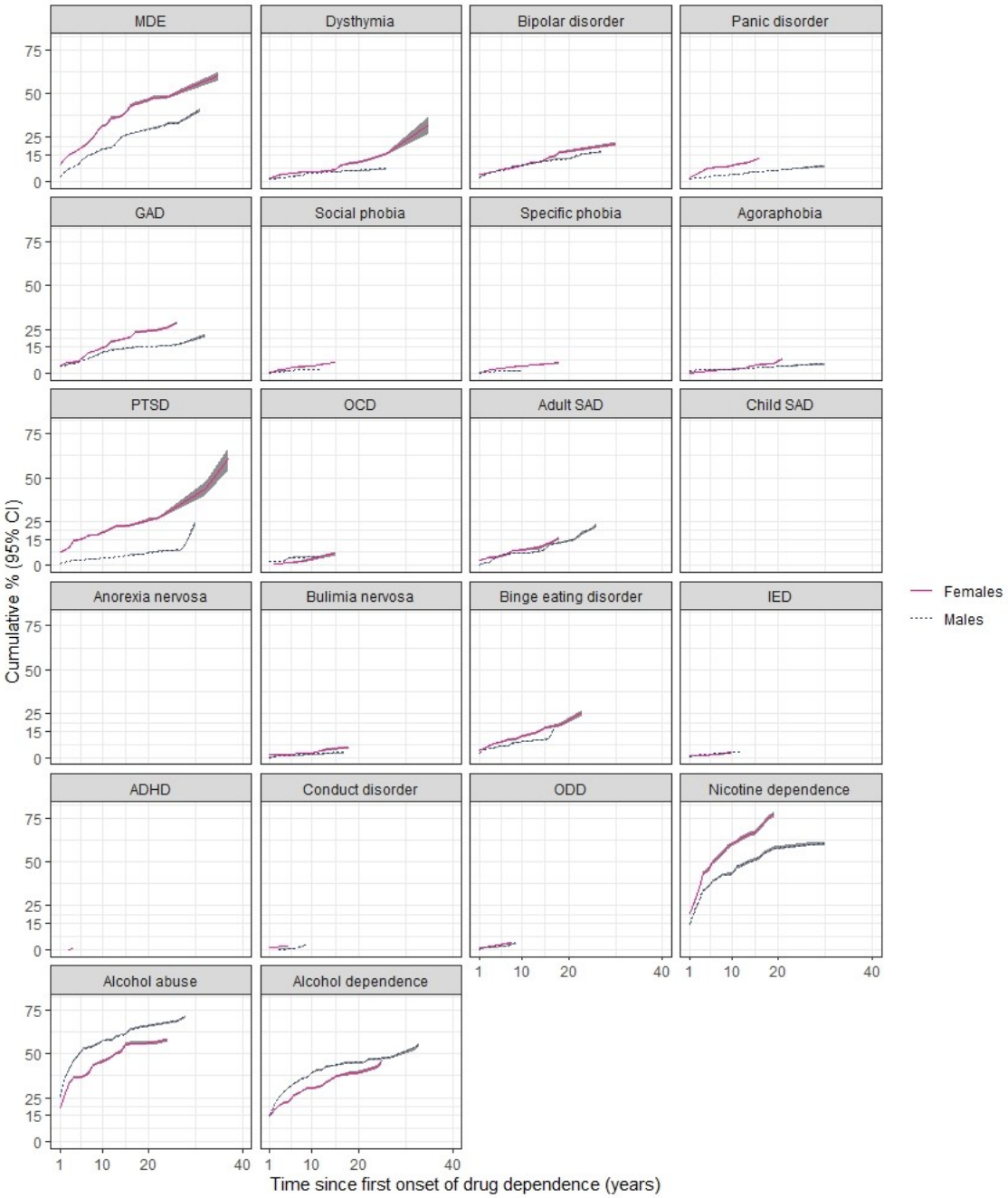


Figure 5x. Sex-specific absolute risks of later disorders after the initial onset of drug dependence



Supplementary Figure 6. Absolute risks (time-specific estimate)

Absolute risk of later disorders after the initial onset of a prior disorder (time-specific estimates)

Each panel shows the overall absolute risks and 95% confidence interval (shaded area) of developing a subsequent later disorder after the onset of prior disorder estimated separately by the age-of-onset for prior disorder ('< 20 years' - blue line in the plot), ('20-40 years' - pink line in the plot), and ('> 40 years' – orange line in the plot). The label for each later disorder is shown at the top of each panel. The horizontal axis shows the time since onset of prior disorder. The vertical axis shows the cumulative incidence proportions per 100 persons (and 95% CI). Abbreviations: Major Depressive Episode – MDE; Generalized Anxiety Disorder – GAD; Attention Deficit Hyperactivity Disorder (ADHD); Obsessive Compulsive Disorder (OCD); Post-Traumatic Stress Disorder (PTSD); Separation Anxiety Disorder (SAD); Intermittent Explosive Disorder (IED); Oppositional Defiant Disorder (ODD).

Figure 6a. Time-specific absolute risks of later disorders after the initial onset of major depressive episode (MDE)

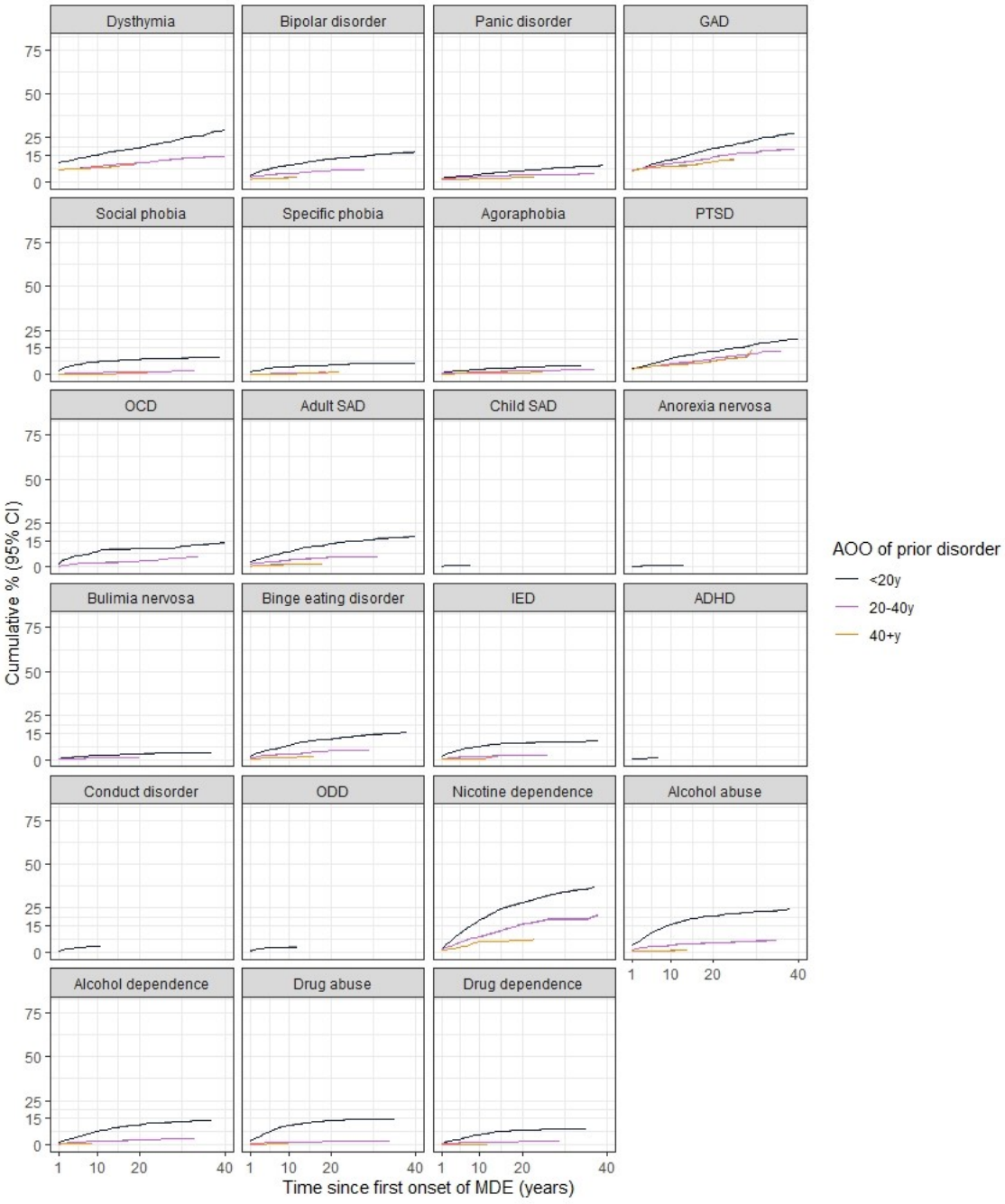


Figure 6b. Time-specific absolute risks of later disorders after the initial onset of bipolar disorder

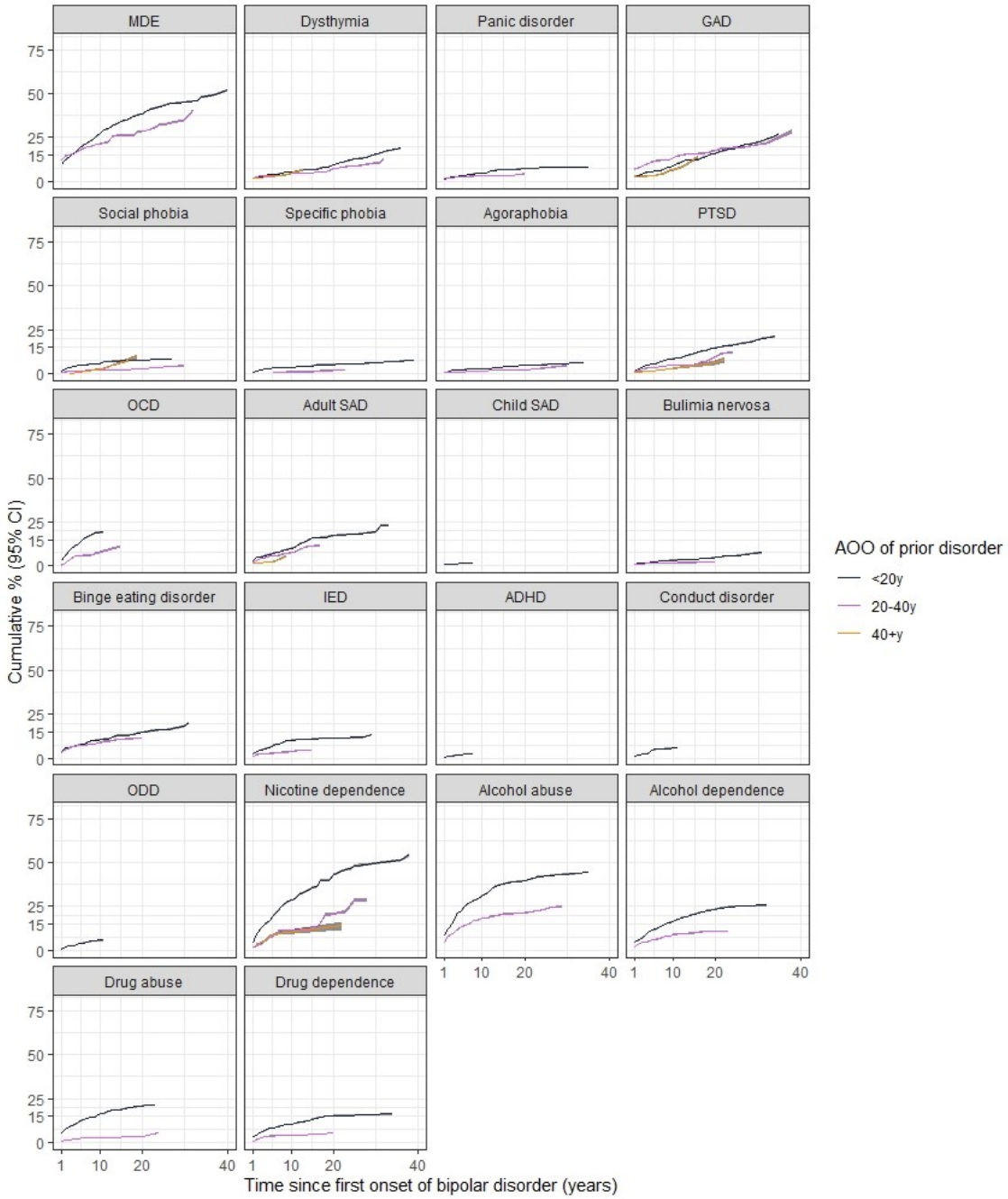


Figure 6c. Time-specific absolute risks of later disorders after the initial onset of dysthymia

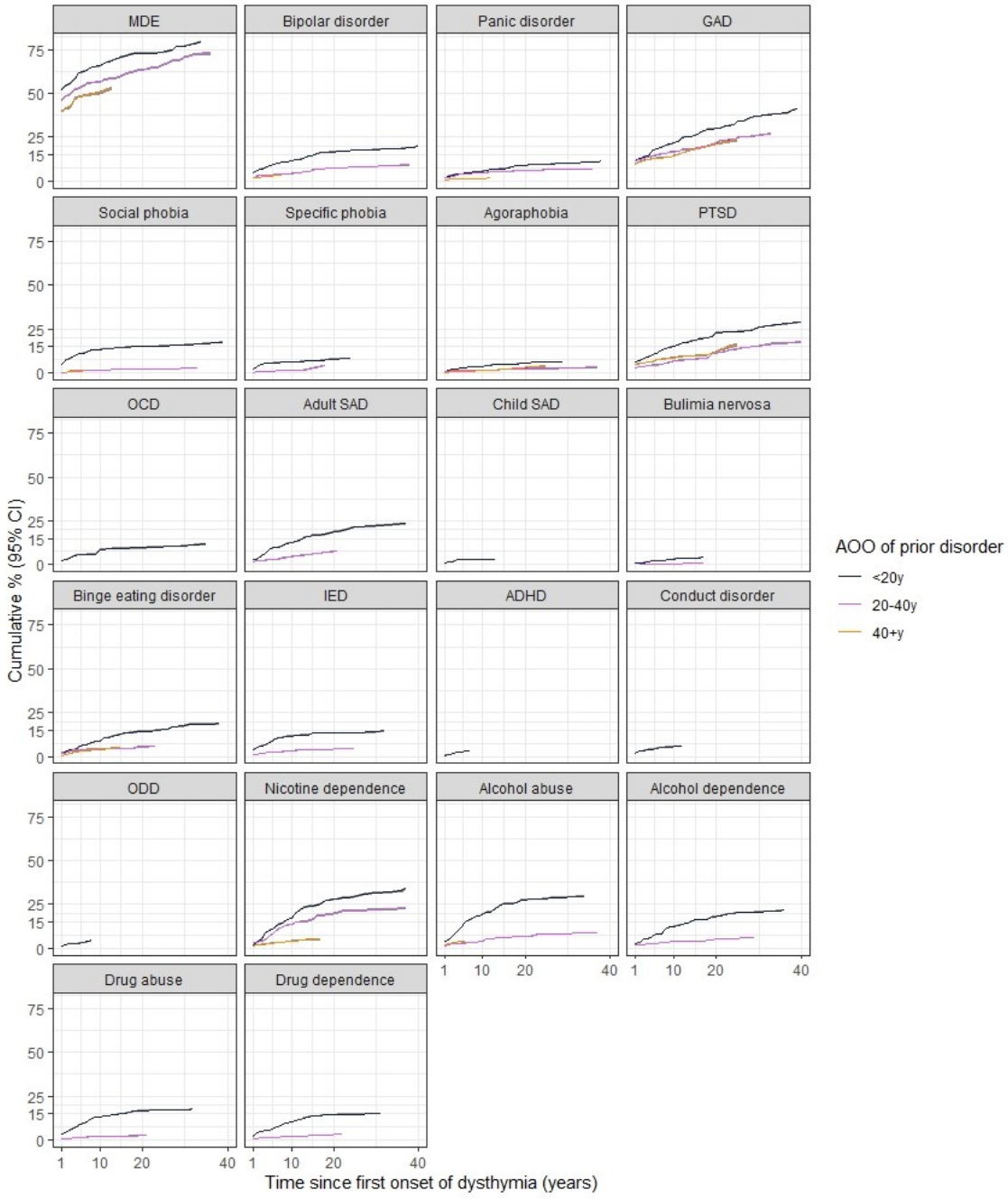


Figure 6d. Time-specific absolute risks of later disorders after the initial onset of panic disorder

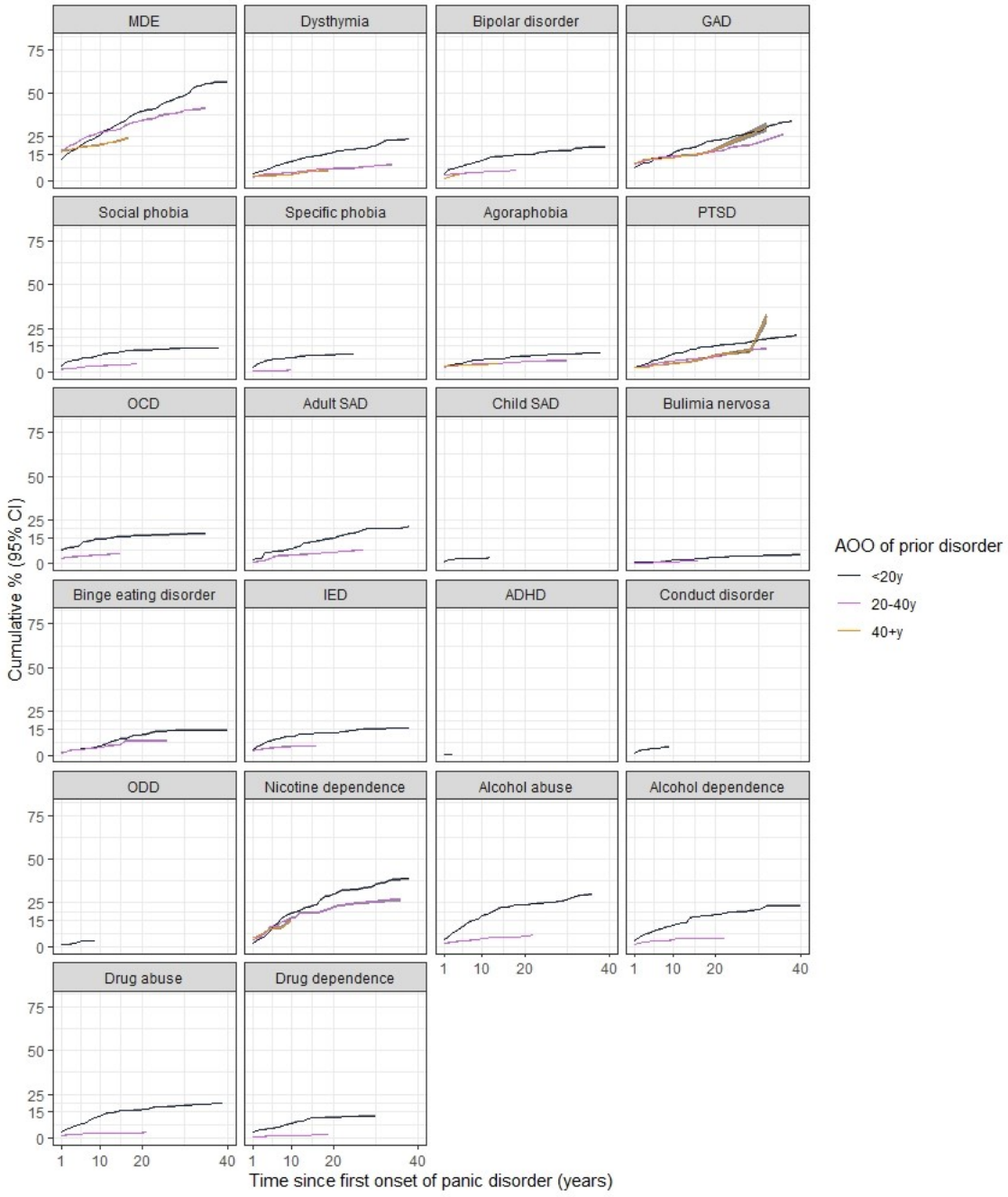


Figure 6e. Time-specific absolute risks of later disorders after the initial onset of generalized anxiety disorder (GAD)

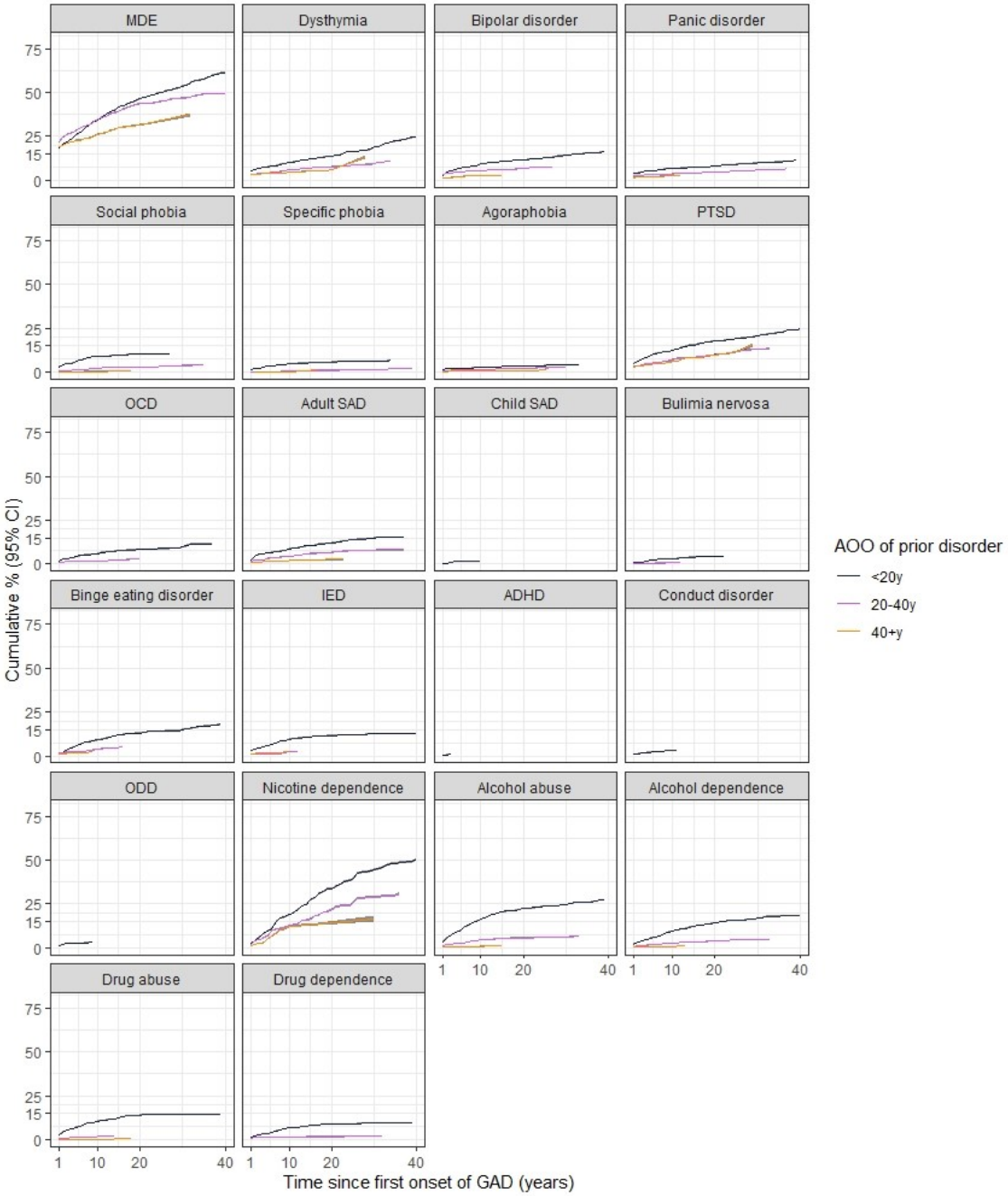


Figure 6f. Time-specific absolute risks of later disorders after the initial onset of social phobia

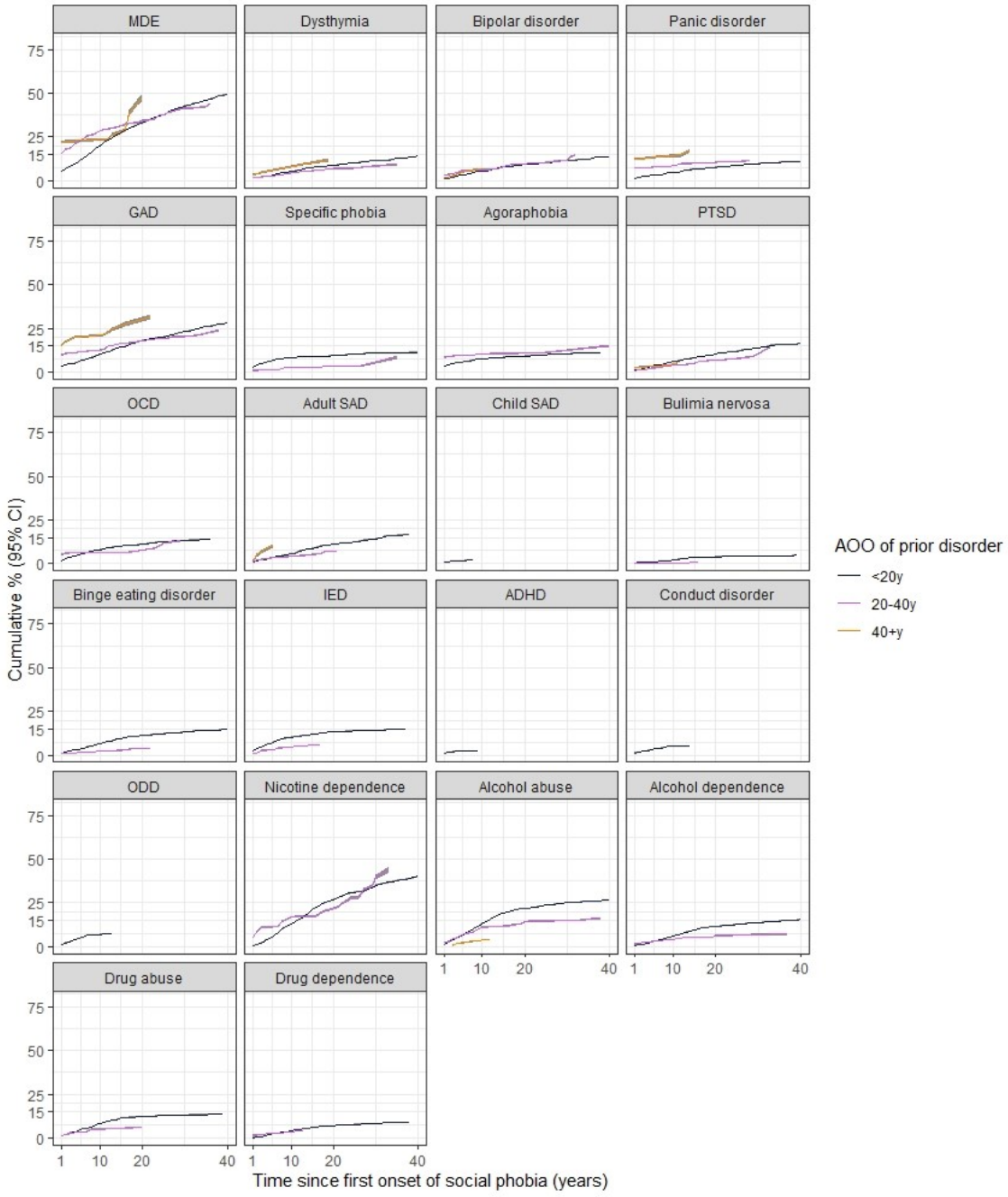


Figure 6g. Time-specific absolute risks of later disorders after the initial onset of specific phobia

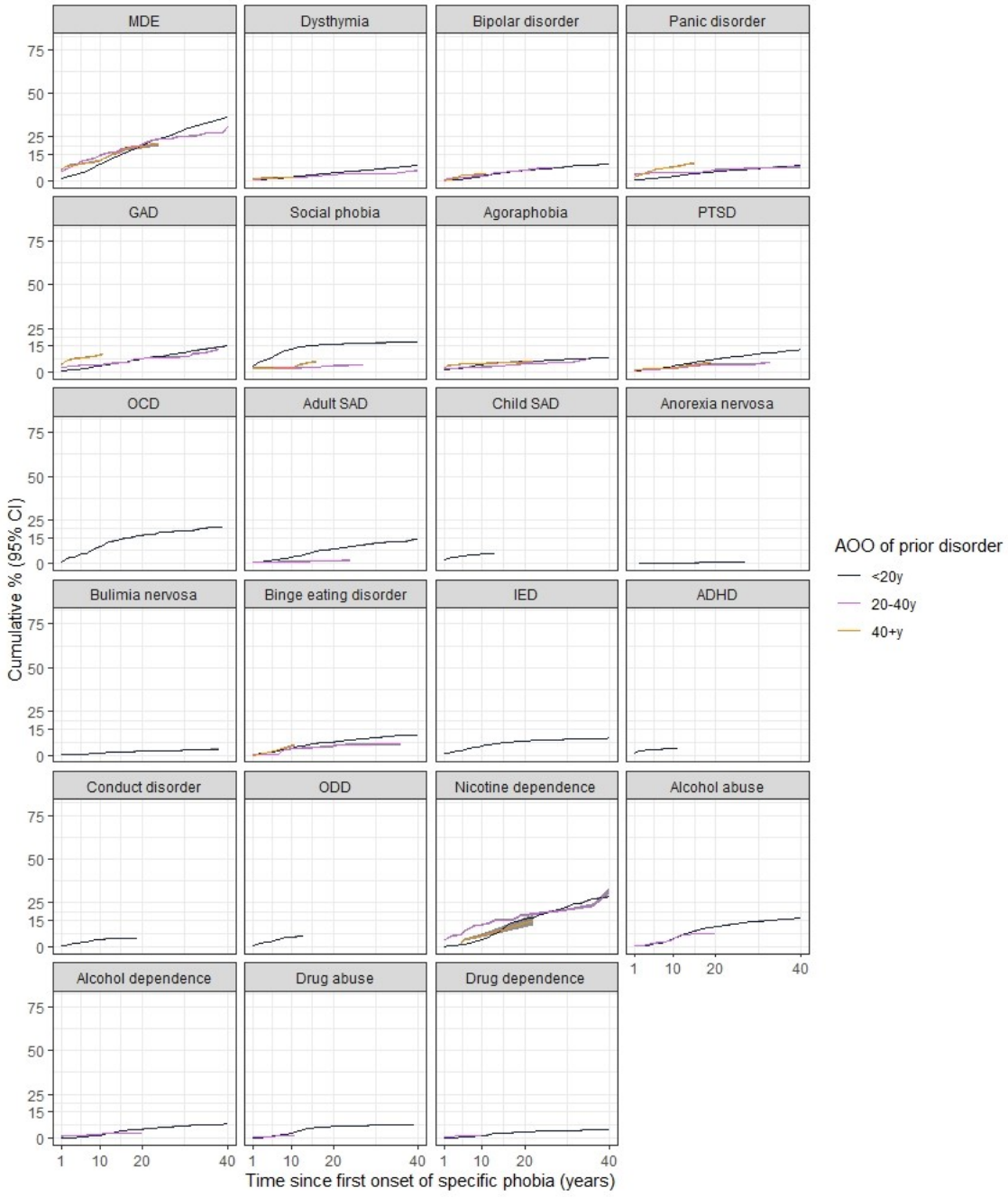


Figure 6h. Time-specific absolute risks of later disorders after the initial onset of agoraphobia

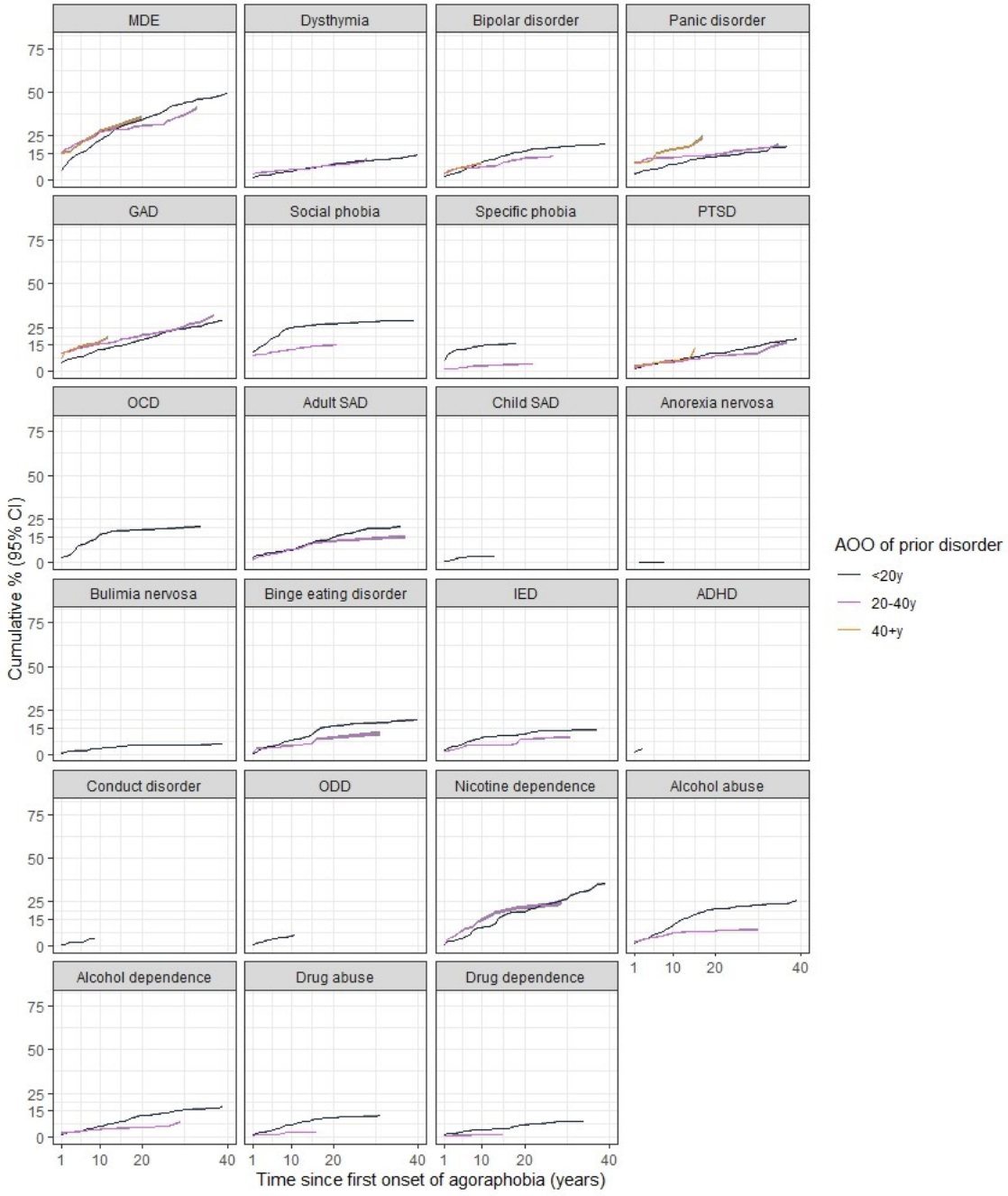


Figure 6i. Time-specific absolute risks of later disorders after the initial onset of post-traumatic stress disorder (PTSD)

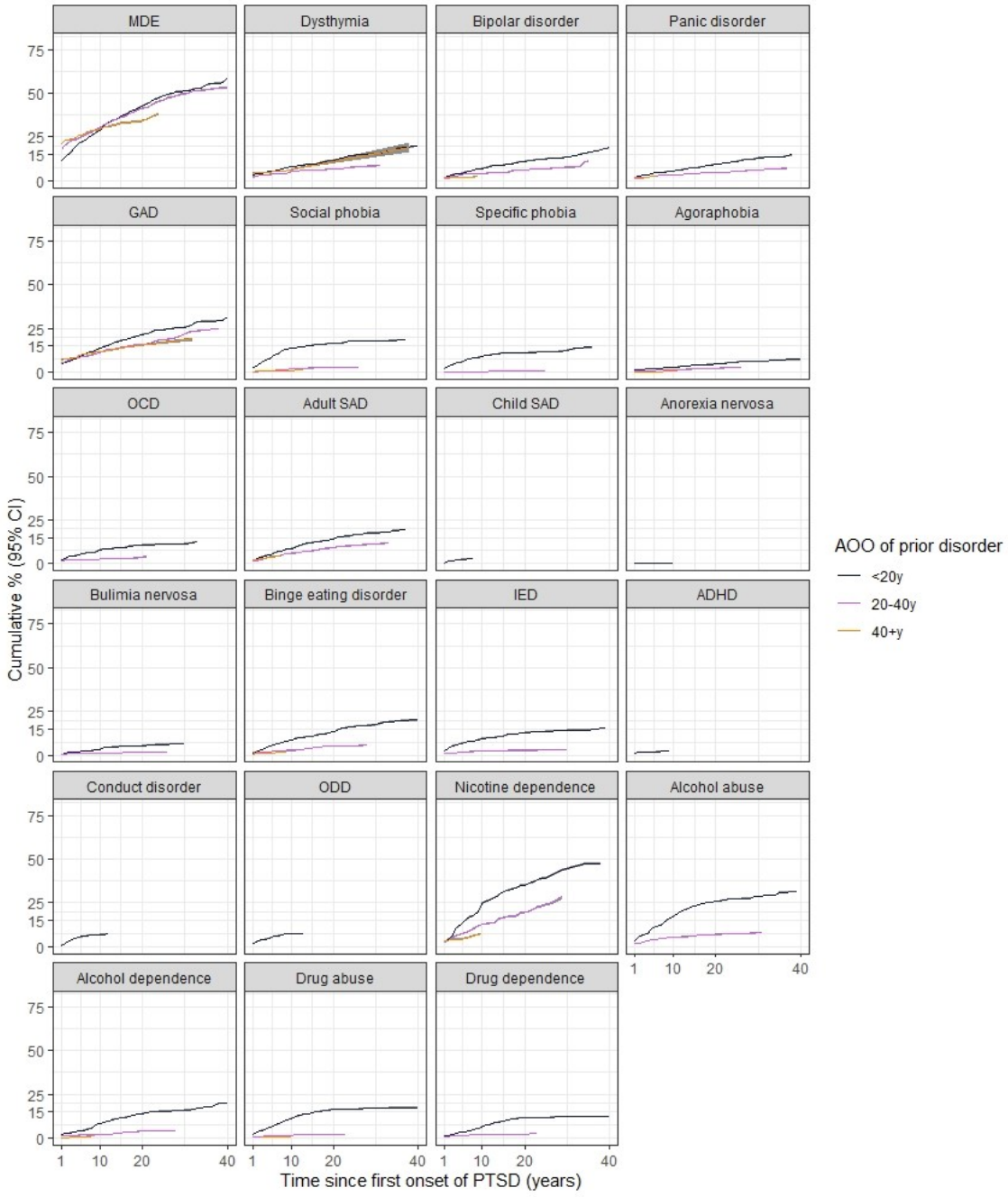


Figure 6j. Time-specific absolute risks of later disorders after the initial onset of obsessive compulsive disorder (OCD)

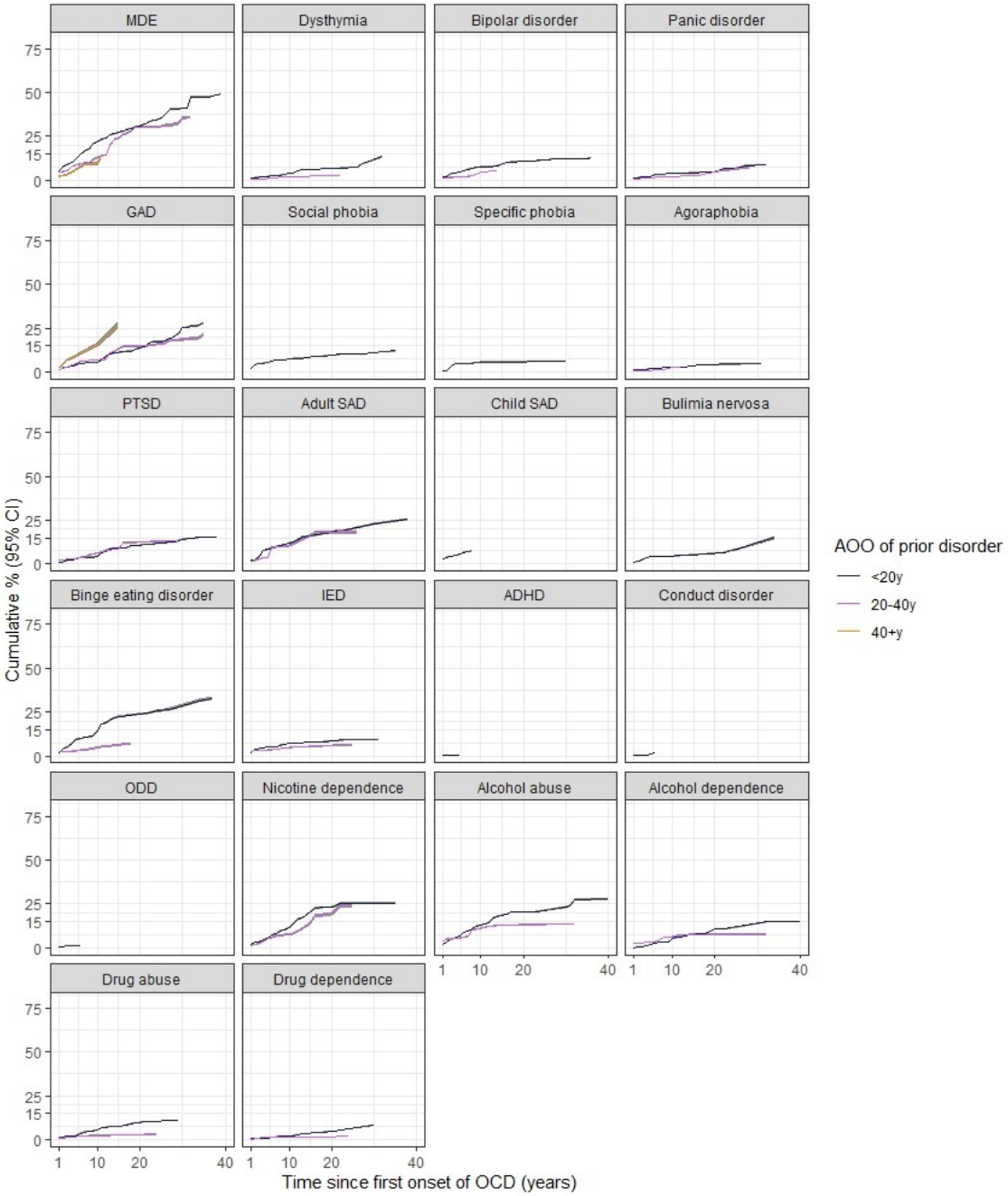


Figure 6k. Time-specific absolute risks of later disorders after the initial onset of adult separation anxiety disorder

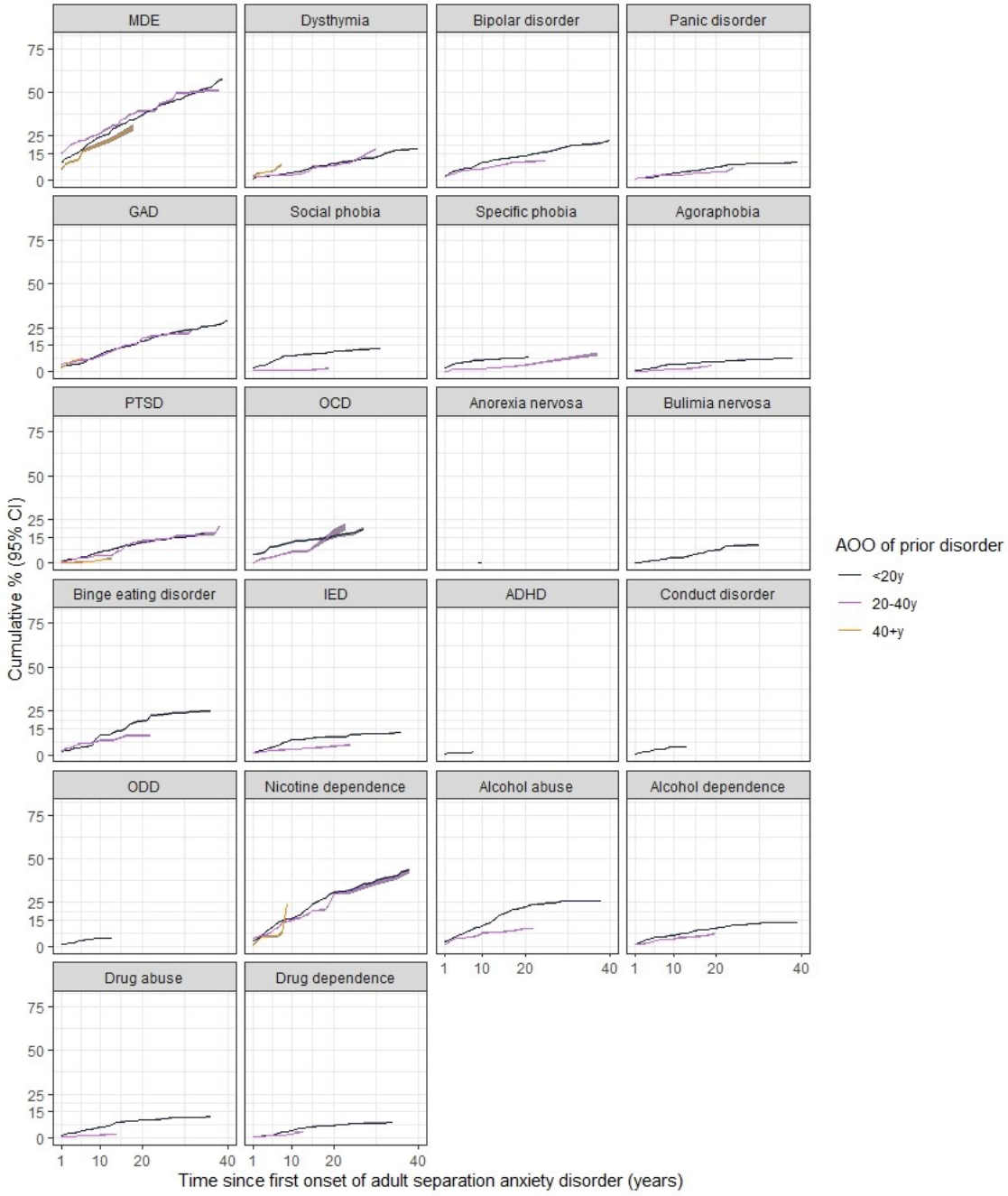


Figure 6l. Time-specific absolute risks of later disorders after the initial onset of child separation anxiety disorder

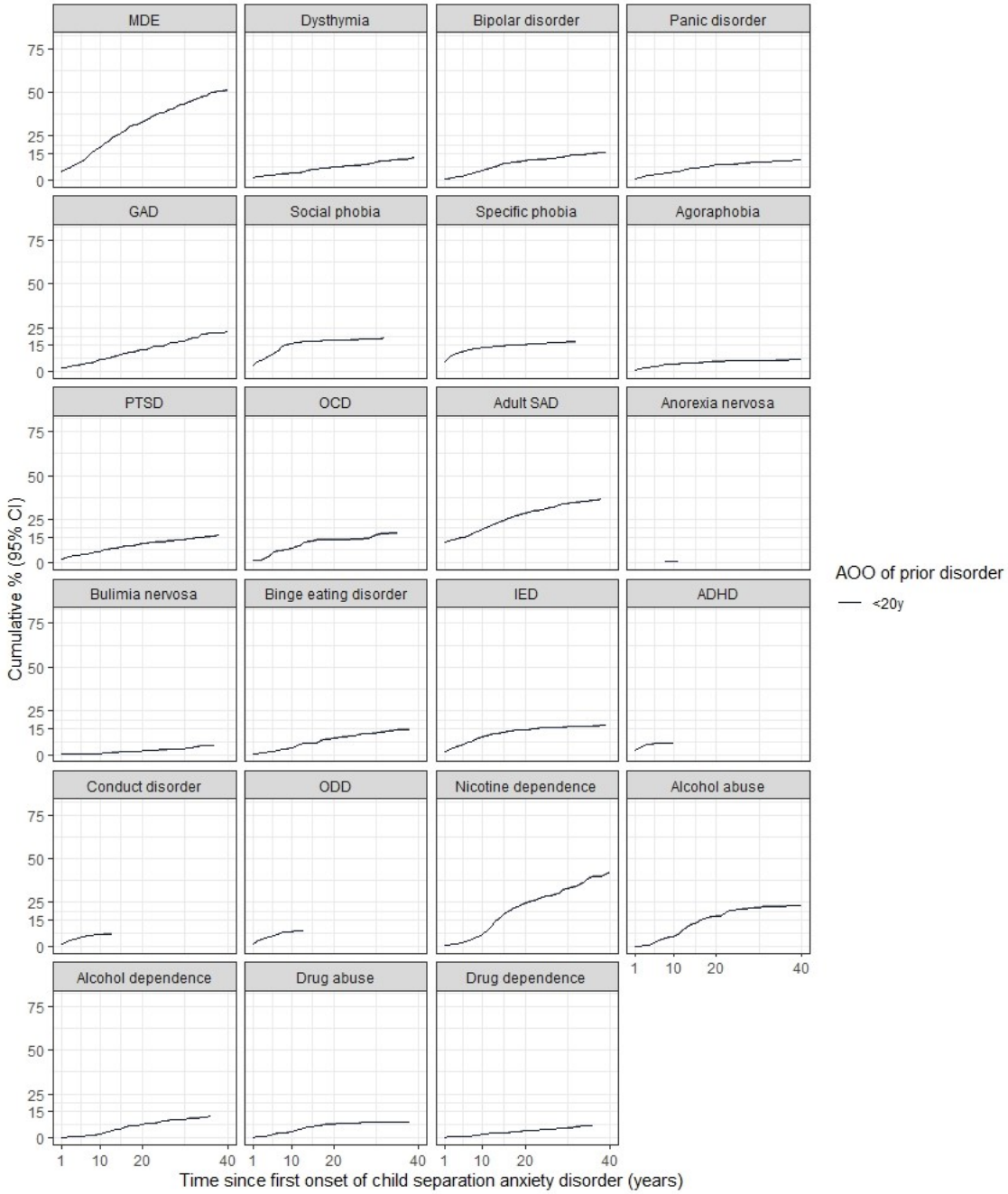


Figure 6m. Time-specific absolute risks of later disorders after the initial onset of anorexia nervosa

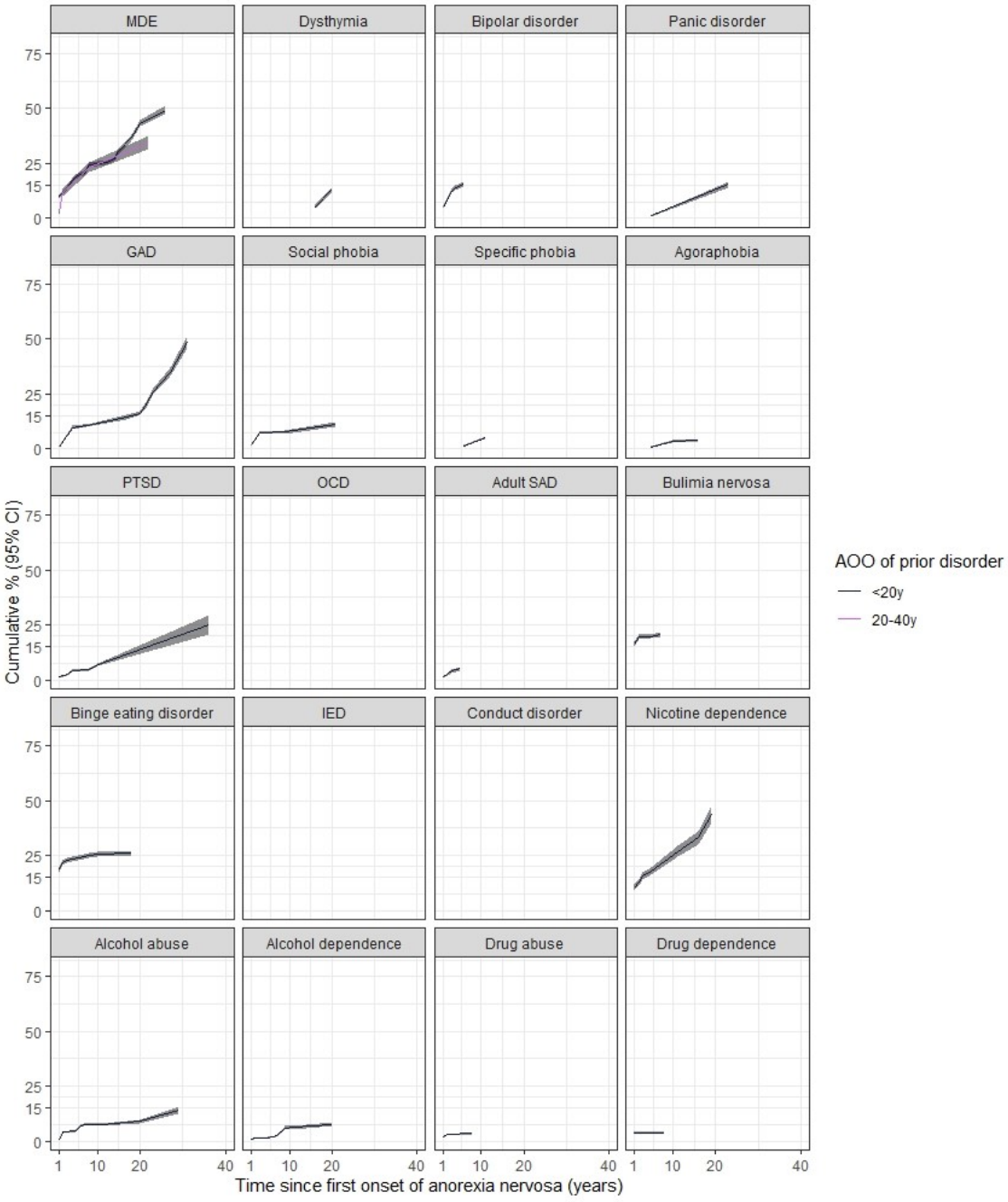


Figure 6n. Time-specific absolute risks of later disorders after the initial onset of bulimia nervosa

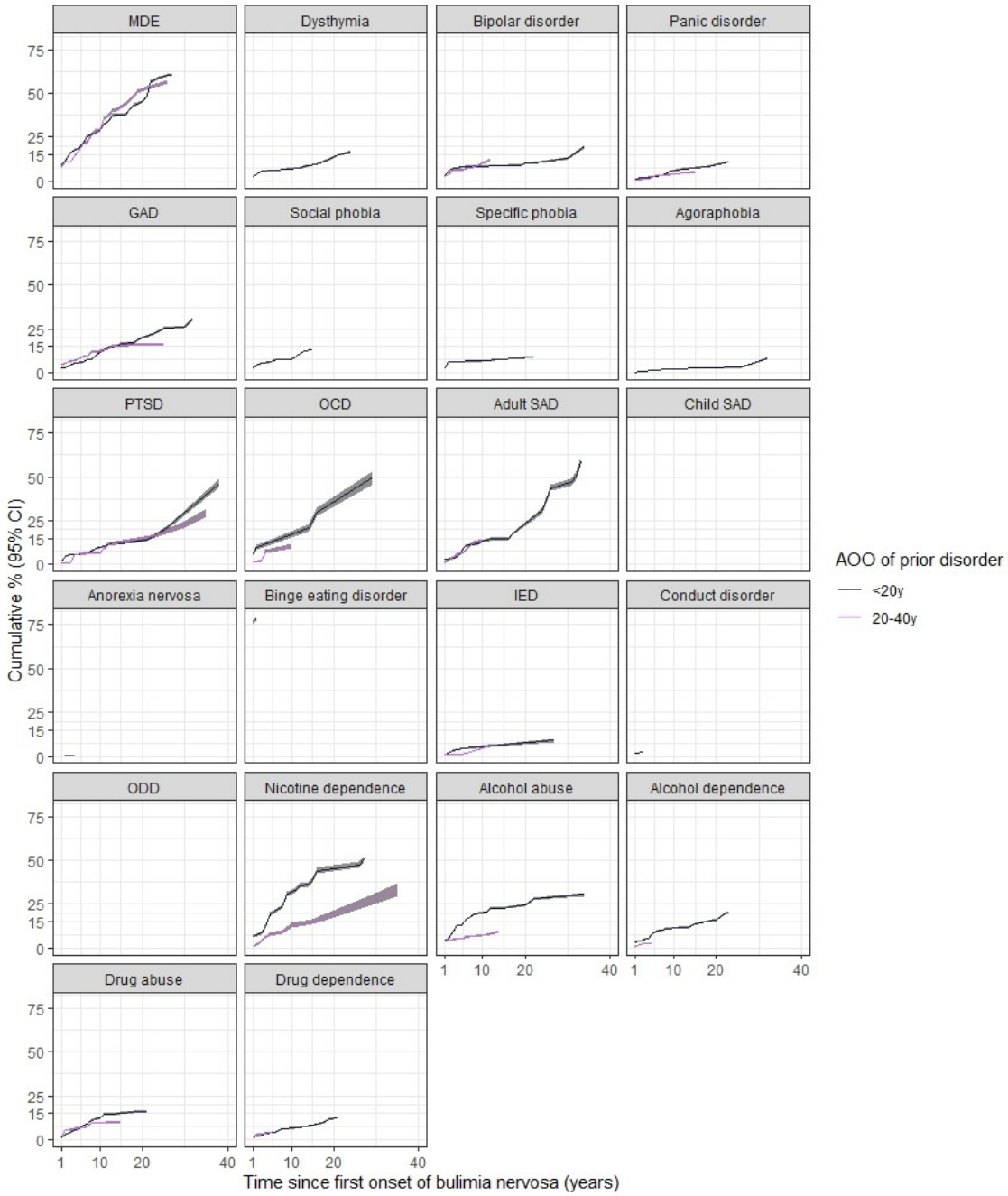


Figure 6o. Time-specific absolute risks of later disorders after the initial onset of binge eating disorder

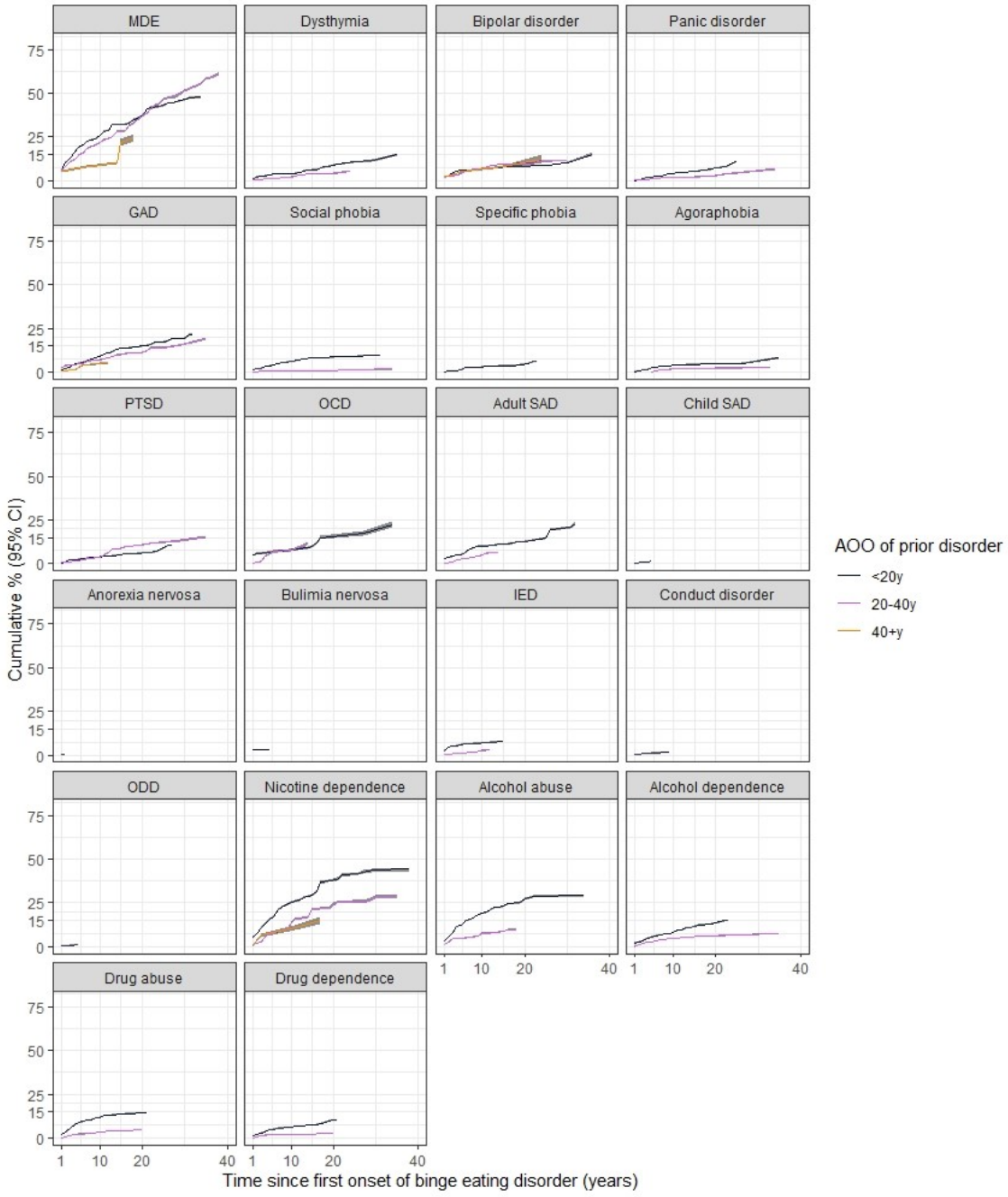


Figure 6p. Time-specific absolute risks of later disorders after the initial onset of intermittent explosive disorder (IED)

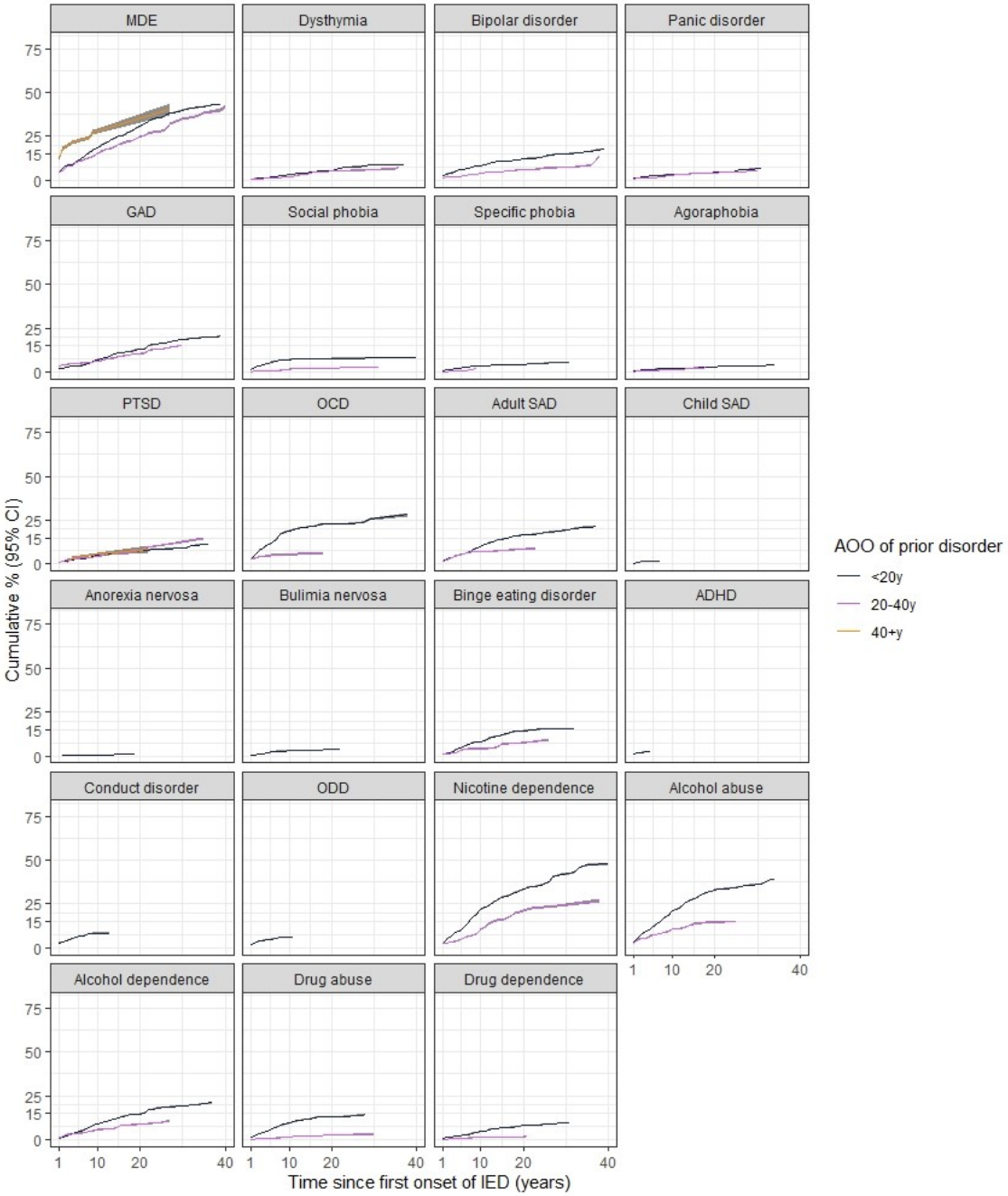


Figure 6q. Time-specific absolute risks of later disorders after the initial onset of attention deficit hyperactivity disorder (ADHD)

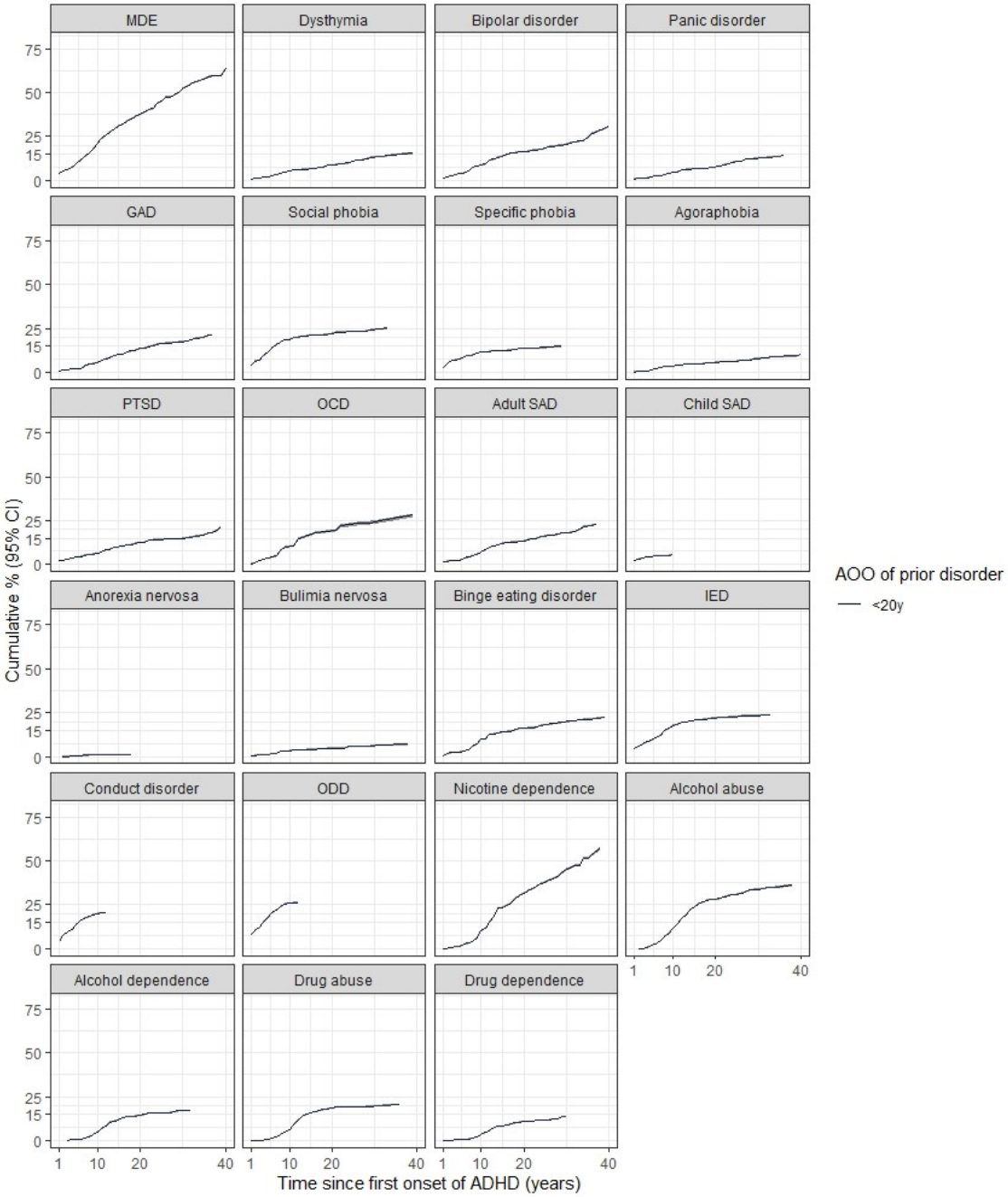


Figure 6r. Time-specific absolute risks of later disorders after the initial onset of conduct disorder

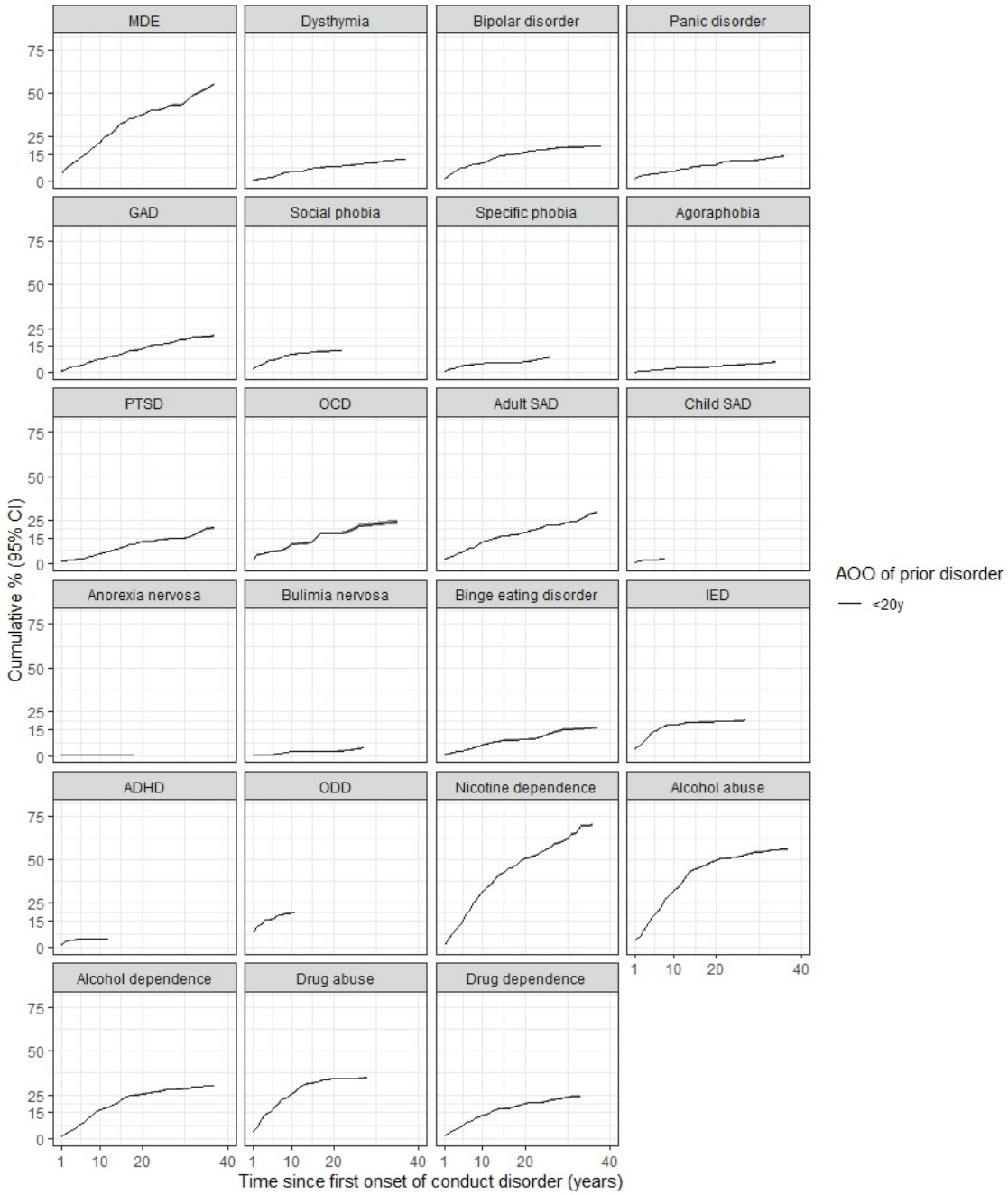


Figure 6s. Time-specific absolute risks of later disorders after the initial onset of oppositional defiant disorder (ODD)

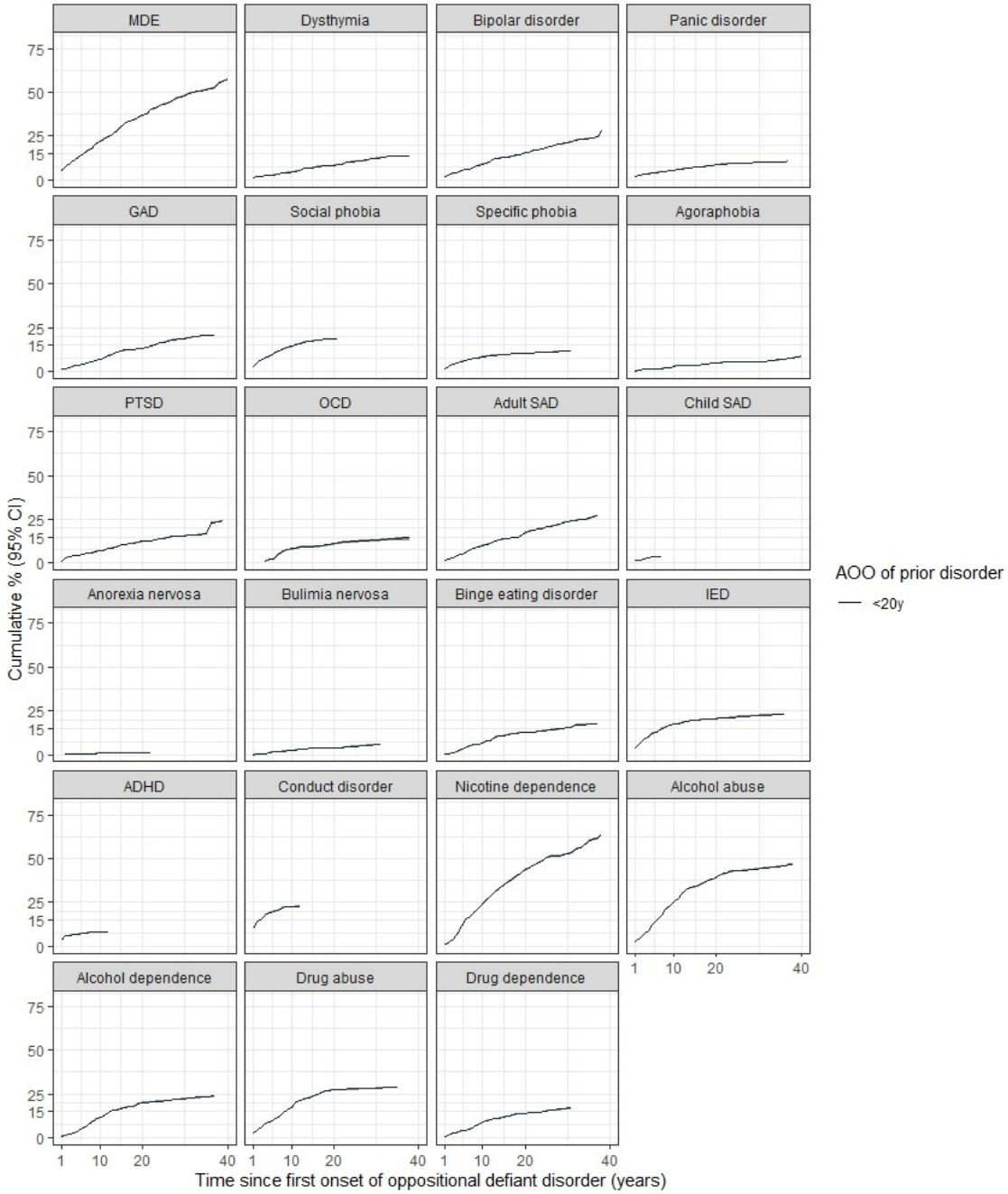


Figure 6t. Time-specific absolute risks of later disorders after the initial onset of nicotine dependence

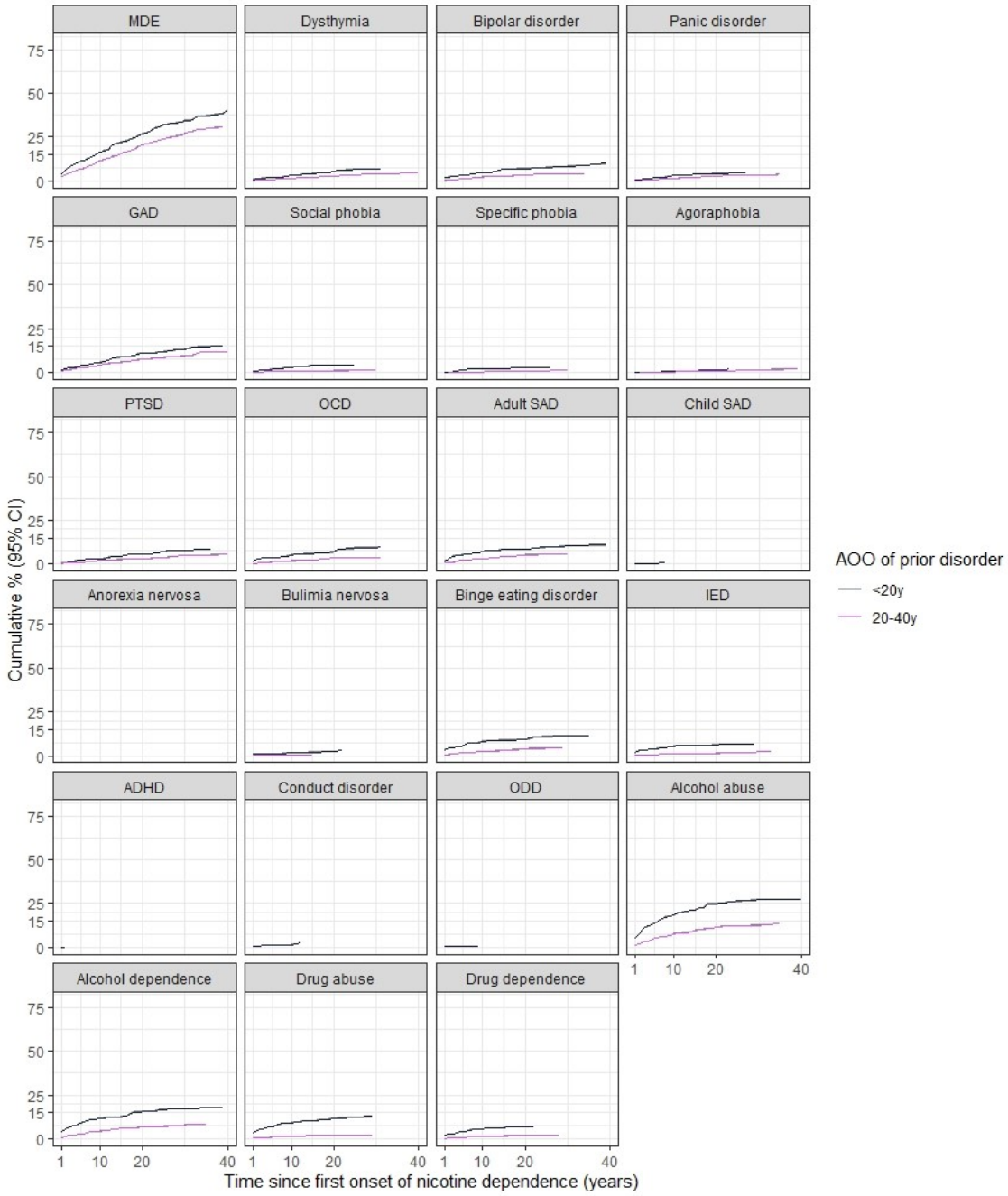


Figure 6u. Time-specific absolute risks of later disorders after the initial onset of alcohol abuse

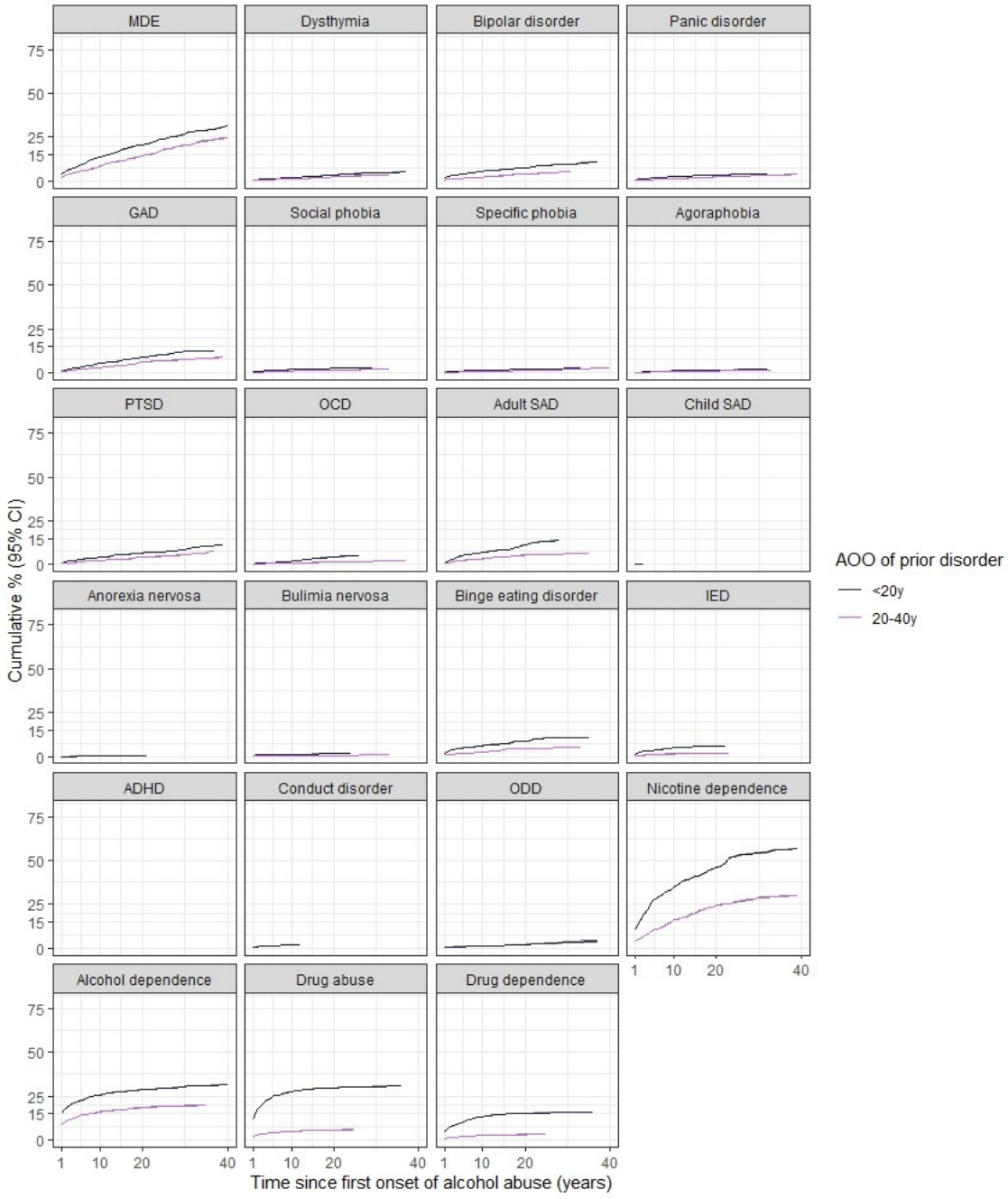


Figure 6v. Time-specific absolute risks of later disorders after the initial onset of alcohol dependence

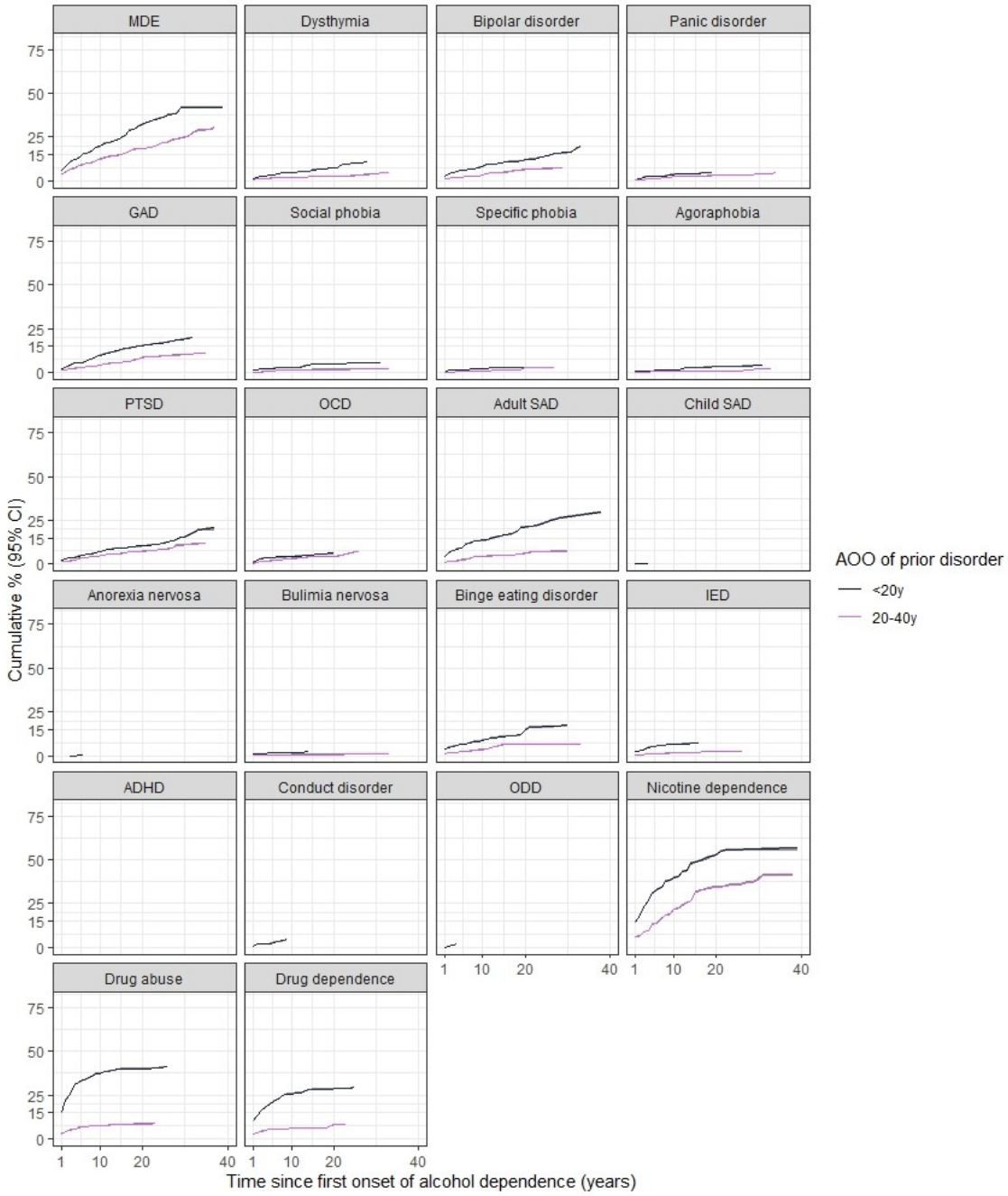


Figure 6w. Time-specific absolute risks of later disorders after the initial onset of drug abuse

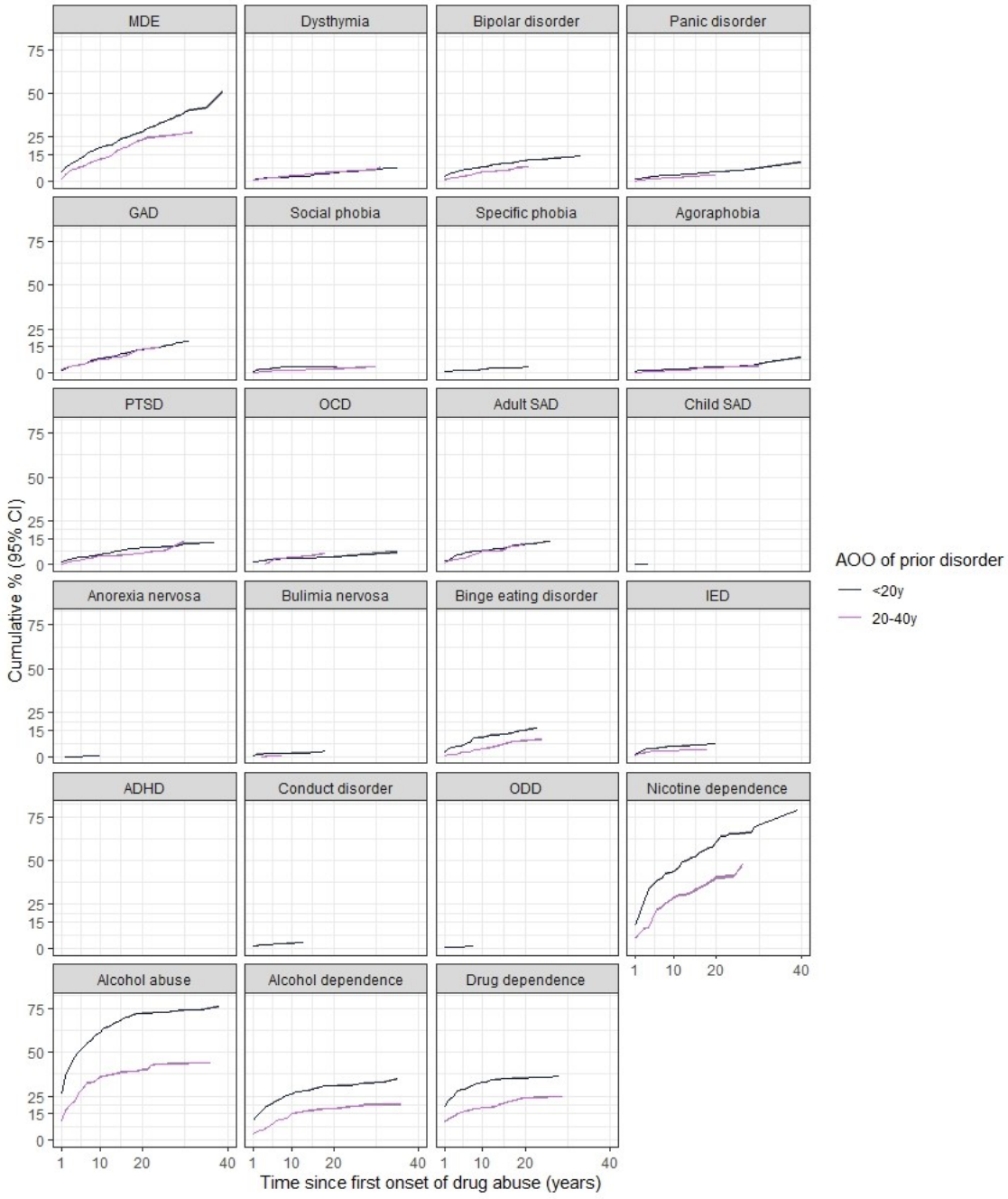
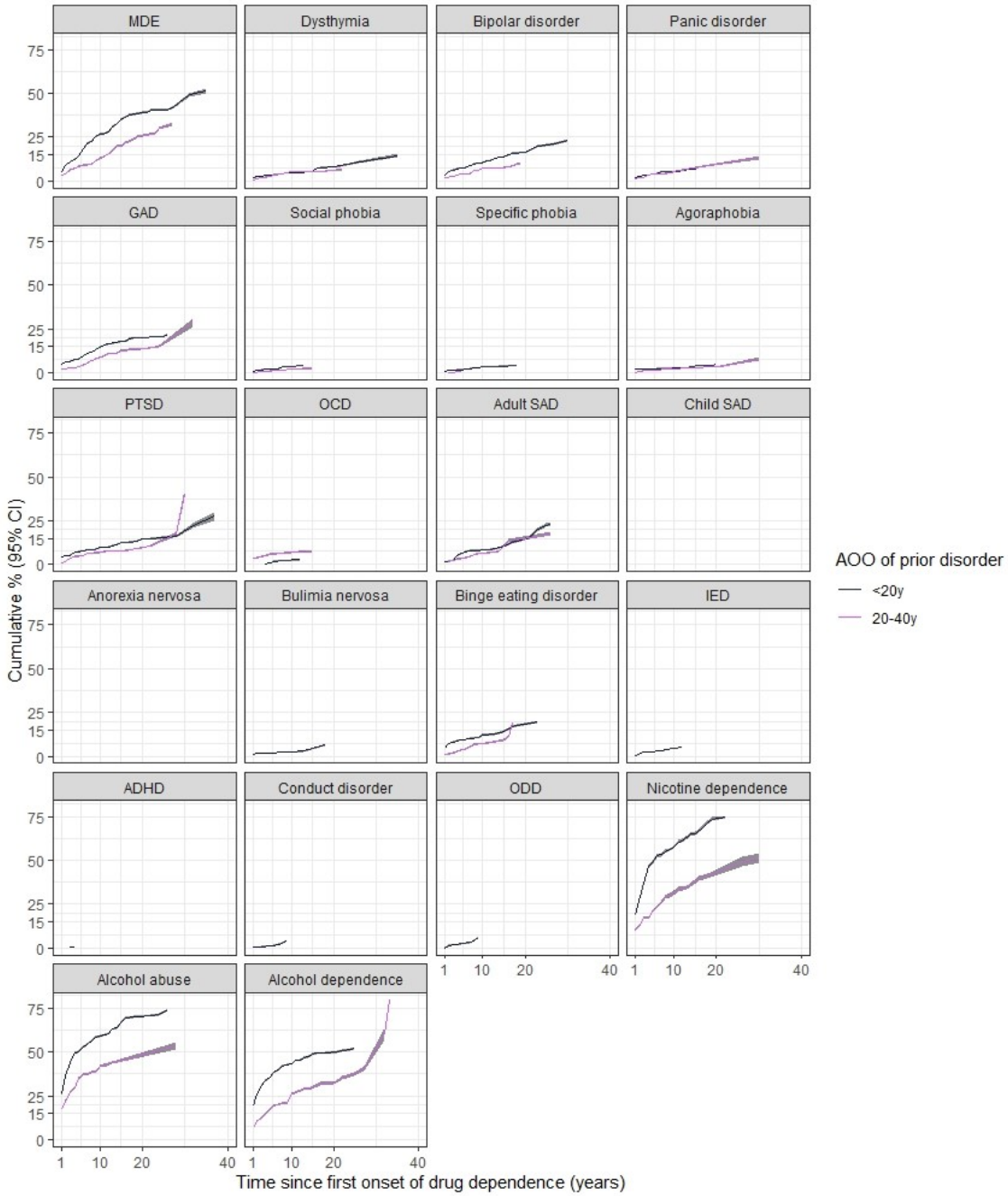


Figure 6x. Time-specific absolute risks of later disorders after the initial onset of drug dependence



Additional methods

In most countries, internal subsampling was used to reduce respondent burden and average interview time by dividing the interview into two parts. Part 1 of the interview, administered to all respondents, evaluated core mental disorders (depression, mania, panic disorder, specific phobia, social phobia, agoraphobia, GAD and substance-use disorder). Part 2 of the interview, included more information related to correlates and disorders of secondary interest and this was administered to the respondents reporting any core mental disorder and a probability sample of part 1 respondents who did not meet criteria for any core disorder. Sample sizes of these surveys ranged from 2,357 (Romania) to 12,790 (New Zealand). A total of 145,990 respondents completed part 1 of the interview and 80,190 completed part 2 of the interview with an average weighted response rate of 69·5%. Part 2 responses were weighted by the inverse of their probability of selection into part 2 sample to adjust for any differential sampling. Additional weights were used to adjust for differential probabilities of selection within households, nonresponse, and to match the samples to population sociodemographic distributions. Thus, the weighted estimates shown below are representative of the original sampling frame. Further details of the construction of the analyses weights are provided elsewhere (Kessler et al. 2018). Due to concerns about recall failure among adults in the assessment of childhood and adolescence disorders, Oppositional Defiant Disorder, Conduct Disorder, Attention Deficit Hyperactivity Disorder and Separation Anxiety Disorder were assessed only among the part 2 respondents aged 18-44 or 18-39. We did not quantify the association between (a) prior substance dependence and later substance abuse, and (b) prior adult separation anxiety disorder and subsequent child separation anxiety disorder as the first disorder over-rides the later disorder. Estimates were not quantified for disorder pairs with less than 30 cases due to unstable estimates. The WMH surveys assessed age of onset of disorders in whole years, and respondents may report occurrences of two or more disorders in any given year (i.e. presence of ties). In a time-to-event framework, these ties would lead to under-reporting of comorbidity between disorders that occur in the same year. In keeping with our previous analyses (Plana-Ripoll et al. 2019), we broke these ties by randomly reassigning a proportion of those with same year of onset to having the prior disorder a year earlier. Before estimating each pairwise association, we calculated the proportion of respondents that had to be randomly reassigned in the total sample by dividing the number of respondents that developed 'prior disorder' before 'later disorder' by the number of respondents with both 'prior disorder' and 'later disorder' excluding those with ties. This proportion was multiplied with the number of respondents with ties (i.e. two disorders with the same year of onset) to obtain the number to be randomly assigned to having the prior disorder a year earlier.

References

Kessler, R. C., Heeringa, S. G., Pennell, B., Sampson, N. A., Zaslavsky, A. M. (2018). Methods of the World Mental Health Surveys. *Mental Disorders Around the World - Facts and Figures from the WHO World Mental Health Surveys*. K. M. Scott, P. de Jonge, D. J. Stein et al. Cambridge, UK: Cambridge University Press**:** 9-40.

Plana-Ripoll, O., Pedersen, C. B., Holtz, Y., Benros, M. E., Dalsgaard, S., de Jonge, P., Fan, C. C., Degenhardt, L., Ganna, A., Greve, A. N., Gunn, J., Iburg, K. M., Kessing, L. V., Lee, B. K., Lim, C. C. W., Mors, O., Nordentoft, M., Prior, A., Roest, A. M., Saha, S., Schork, A., Scott, J. G., Scott, K. M., Stedman, T., Sorensen, H. J., Werge, T., Whiteford, H. A., Laursen, T. M., Agerbo, E., Kessler, R. C., Mortensen, P. B., McGrath, J. J. (2019). Exploring Comorbidity Within Mental Disorders Among a Danish National Population. *JAMA Psychiatry*, **76**, 259-270.