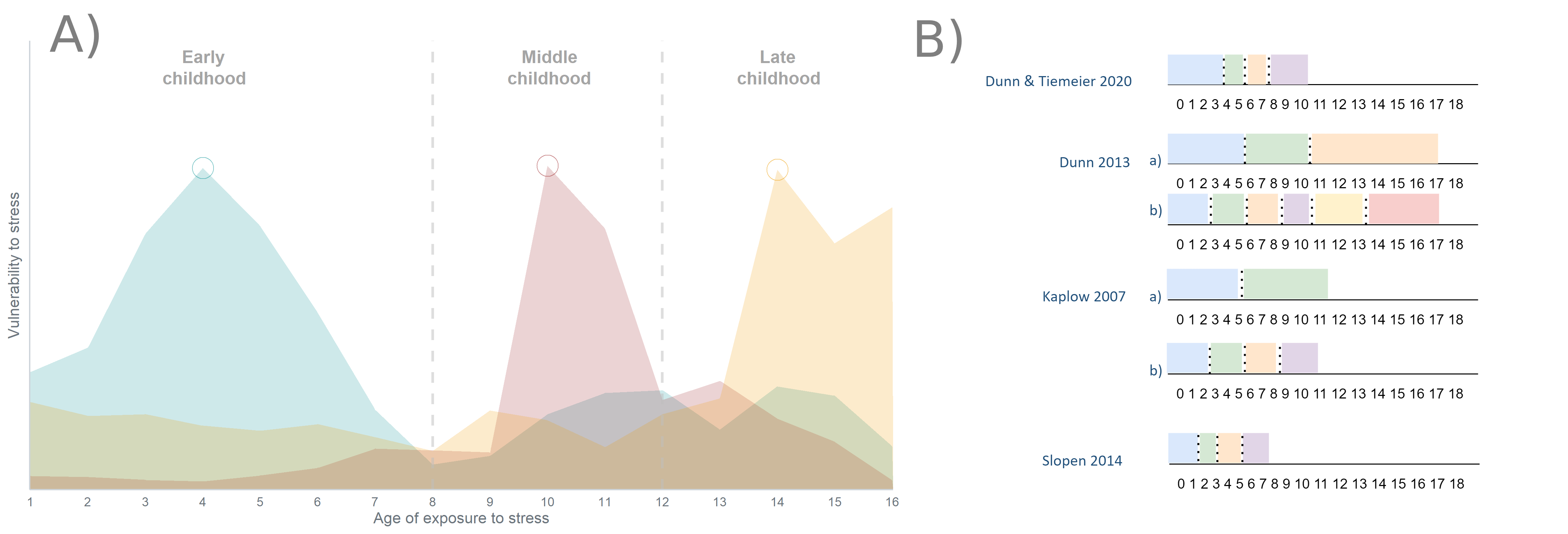
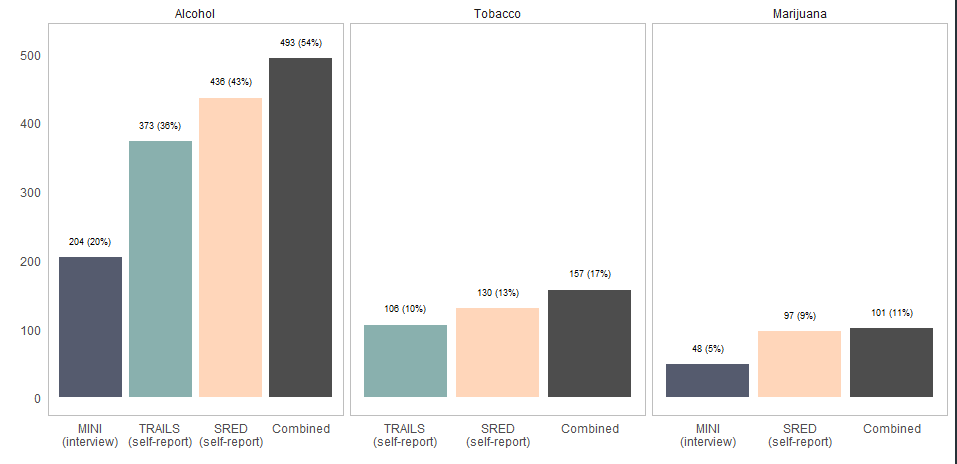
Appendix

Appendix Figure 1. A) Neurovulnerability to stress across key brain structures according to age of exposure to stress as theorized by neurological research. Figure based on simulated data to adapt from Kirsch, Nemeroff and Lippard (2020). B) Age groups used in adversity literature to categorize adverse life events according to when they happened.

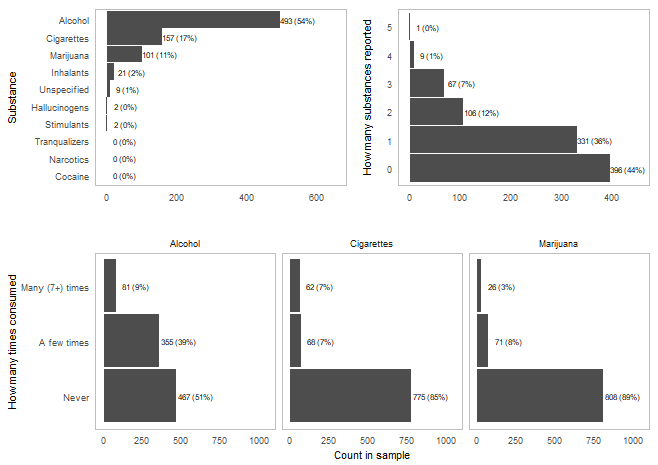


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| Appendix Table 1. Detailed counts and percentages of each adverse life event (ALE) which combined and summed produce a total ALE score | |
| **Adverse life event** | **n (%)** |
| Moved homes | 546 (60.0%) |
| Switched schools | 246 (27%) |
| Hospitalized | 412 (45.3%) |
| Mother seriously ill | 426 (47.1%) |
| Mother hospitalized | 441 (48.5%) |
| Father seriously ill | 253 (28.0%) |
| Father hospitalized | 184 (20.2%) |
| Sibling seriously ill | 149 (16.4%) |
| Close friend seriously ill | 23 (2.5%) |
| Death in the family | 25 (2.8%) |
| Death outside the family | 7 (2.4%) |
| Parental divorce | 285 (31.4%) |
| Extended living outside of household | 23 (2.5%) |
| Physical violence | 209 (23.0%) |
| Sexual abuse | 49 (5.4%) |

**Combining substance use instruments:** To combine measurements from the three instruments and end up with a total substance count score, we first dichotomized the responses from the SRED instrument. The response options were “Never”, “Once”, “2-3 times”, “4-6 times” and “7 or more times”. Responses which were not “Never” were recoded as “yes” having used the substance. Second, we used questions from the MINI-KID, which inquired whether the adolescent used one of 6 drugs over the past year with the intention of getting high. Those included marijuana, inhalants, stimulants, hallucinogens, cocaine or narcotics. The response was binary “yes/no” coded. The MINI-KID also provided a question on alcohol, which asked if the adolescent drank 3 or more glasses of alcohol in within 3 hours in a single day and if this happened more than 3 times in the past year. If the adolescent responded affirmative to all alcohol questions, the interviewer coded alcohol usage as “yes”. Third, we used three questions referring to substance use based on a questionnaire used in the TRAILS study. They inquired if adolescents ever smoked, drank a glass of alcohol or took any drugs. The possible responses are again binary “yes/no”. The questions about overlapping substances were collapsed across questionnaires, so that if an adolescent responded with a “yes” on any one questionnaire for a given substance, they are coded as having taken the substance. For example, if an adolescent responds with a “no” on the SRED but “yes” on the MINI-KID, the response is coded as “yes”. For the TRAILS question on “other drugs”, the response was only coded as “yes” if no other drug was taken. The final count variable was a sum of number of substances the adolescent responded “yes” to. Appendix Figure A below (not referred to in main text) illustrates which instruments contained information about which substance and respective frequency counts of substance use for each:



Appendix Figure A. Frequency counts for substances which were measured using multiple instruments. Presented in black the combined value obtained from all instruments which was used in the final analysis.

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Appendix Figure 2. Counts and percentages of number and frequency of substances used by adolescents in the current sample

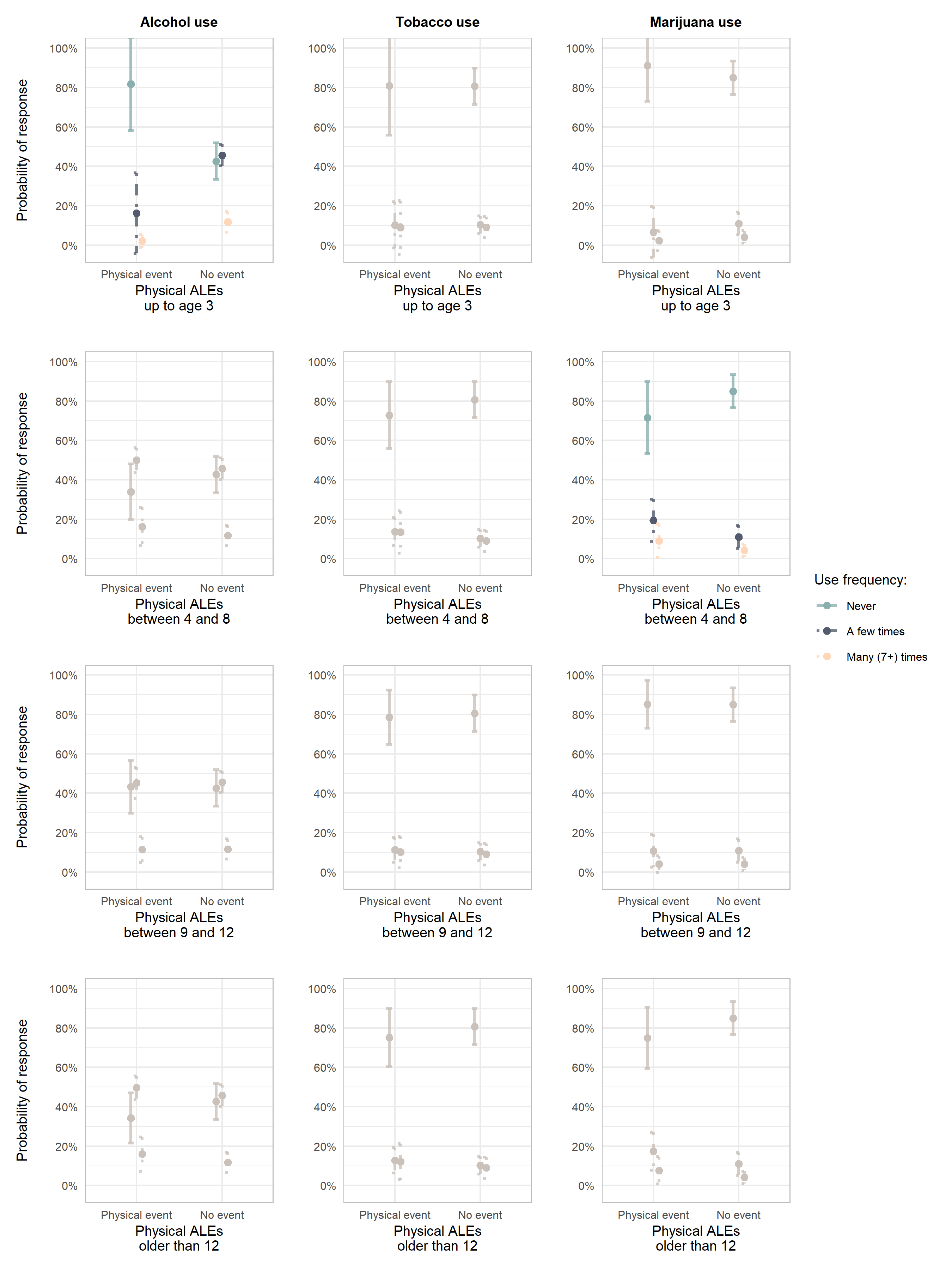
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| Appendix Table 2. Incidence rate ratio (IRR) Poisson coefficient estimates from modelling the effect of broad adverse life events (ALE) on number of substances used | | | | | | | | | | |
|  | **Bivariate model** | | | | **Adjusted model** | | | **Split by age periods model** | | |
| **IRR** | | **95% CI** | **p-value** | **IRR** | **95% CI** | **p-value** | **IRR** | **95% CI** | **p-value** |
| ALE lifetime | 1.07 | | [1.03, 1.12] | < .001 | 1.03 | [0.98, 1.07] | 0.255 |  |  |  |
| ALE before 3 | |  |  |  |  |  |  | 1.01 | [0.92, 1.10] | 0.890 |
| ALE 4 To 8 | |  |  |  |  |  |  | 0.98 | [0.91, 1.06] | 0.626 |
| ALE 9 To 12 | |  |  |  |  |  |  | 1.01 | [0.94, 1.08] | 0.784 |
| ALE Older Than 12 | |  |  |  |  |  |  | 1.05 | [0.97, 1.14] | 0.193 |
| Age, years | |  |  |  | 1.37 | [1.26, 1.50] | < .001 | 1.37 | [1.26, 1.49] | < .001 |
| Sex (Female) *1* | |  |  |  | 0.94 | [0.82, 1.08] | 0.405 | 0.94 | [0.82, 1.09] | 0.415 |
| National origin  (Non-Dutch) *1* | |  |  |  | 0.88 | [0.73, 1.07] | 0.201 | 0.88 | [0.73, 1.06] | 0.177 |
| Urbanicity of living environment (Rural)*1* | |  |  |  | 1.18 | [0.99, 1.41] | 0.065 | 1.17 | [0.98, 1.40] | 0.081 |
| Urbanicity of living environment (Suburban) | |  |  |  | 1.03 | [0.85, 1.25] | 0.768 | 1.03 | [0.85, 1.25] | 0.727 |
| Household income (€1600 - 2399)*1* | |  |  |  | 1.08 | [0.83, 1.41] | 0.569 | 1.09 | [0.84, 1.42] | 0.532 |
| Household income (€2400 - 4399) | |  |  |  | 0.95 | [0.75, 1.20] | 0.673 | 0.96 | [0.75, 1.21] | 0.706 |
| Household income (>€4400) | |  |  |  | 0.88 | [0.68, 1.15] | 0.364 | 0.88 | [0.68, 1.15] | 0.365 |
| Parental BSI score | |  |  |  | 1.16 | [0.77, 1.74] | 0.474 | 1.16 | [0.77, 1.74] | 0.475 |
| Parental drug score | |  |  |  | 1.43 | [1.00, 2.04] | 0.050 | 1.40 | [0.98, 2.00] | 0.061 |
| *1*Reference category for sex is “male”; for national origin “Dutch”; for urbanicity “urban”; for househiold “<€1600” | | | | | | | | | | |

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| Appendix Table 3. Incidence rate ratio (IRR) Poisson coefficient estimates from modelling the effect of physical adverse life events (ALE; consisting of sexual and physical abuse) on number of substances used | | | | | | | | | | |
|  | **Bivariate model** | | | | **Adjusted model** | | | **Split by age periods model** | | |
| **IRR** | | **95% CI** | **p-value** | **IRR** | **95% CI** | **p-value** | **IRR** | **95% CI** | **p-value** |
| Physical ALE lifetime | 1.27 | | [1.11, 1.45] | < .001 | 1.18 | [1.03, 1.35] | 0.019 |  |  |  |
| Physical ALE before 3 | |  |  |  |  |  |  | 0.60 | [0.33, 1.08] | 0.086 |
| Physical ALE 4 To 8 | |  |  |  |  |  |  | 1.23 | [0.95, 1.58] | 0.110 |
| Physical ALE 9 To 12 | |  |  |  |  |  |  | 0.92 | [0.73, 1.17] | 0.503 |
| Physical ALE Older Than 12 | |  |  |  |  |  |  | 1.35 | [1.13, 1.62] | 0.001 |
| Age | |  |  |  | 1.38 | [1.27, 1.50] | < .001 | 1.36 | [1.25, 1.48] | < .001 |
| Sex (Female) *1* | |  |  |  | 0.95 | [0.82, 1.09] | 0.443 | 0.92 | [0.80, 1.07] | 0.283 |
| National origin  (Non-Dutch) *1* | |  |  |  | 0.89 | [0.73, 1.07] | 0.207 | 0.88 | [0.73, 1.07] | 0.193 |
| Urbanicity of living environment (Rural)*1* | |  |  |  | 1.18 | [0.99, 1.41] | 0.068 | 1.19 | [1.00, 1.42] | 0.052 |
| Urbanicity of living environment (Suburban) | |  |  |  | 1.03 | [0.85, 1.25] | 0.741 | 1.06 | [0.88, 1.29] | 0.521 |
| Household income  (€1600 – 2399)*1* | |  |  |  | 1.10 | [0.84, 1.43] | 0.499 | 1.08 | [0.83, 1.40] | 0.583 |
| Household income  (€2400 – 4399) | |  |  |  | 0.95 | [0.75, 1.21] | 0.700 | 0.94 | [0.75, 1.19] | 0.635 |
| Household income (>€4400) | |  |  |  | 0.89 | [0.68, 1.16] | 0.384 | 0.88 | [0.67, 1.14] | 0.327 |
| Parental BSI score | |  |  |  | 1.14 | [0.76, 1.71] | 0.508 | 1.17 | [0.79, 1.75] | 0.428 |
| Parental drug use, any | |  |  |  | 1.42 | [1.00, 2.02] | 0.051 | 1.37 | [0.97, 1.93] | 0.076 |
| *1*Reference category for sex is “male”; for national origin “Dutch”; for urbanicity “urban”; for SES “<€1600” | | | | | | | | | | |

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| Appendix Table 4. Incidence rate ratio (IRR) Poisson coefficient estimates from sensitivity analysis model. Physical adverse life events (ALE) consisting of physical or sexual abuse were dummy coded as occurring for the first time in a given age period window and compared on number of substances used | | | |
|  | **IRR** | **95% CI** | **p-value** |
| Earliest ALE before 3*1* | 0.72 | [0.38, 1.35] | 0.302 |
| Earliest ALE 4 To 8 | 1.29 | [0.99, 1.68] | 0.063 |
| Earliest ALE 9 To 12 | 0.97 | [0.75, 1.25] | 0.811 |
| Earliest ALE Older Than 12 | 1.52 | [1.22, 1.91] | < .001 |
| Age | 1.36 | [1.25, 1.48] | < .001 |
| Sex (Female) *2* | 0.93 | [0.80, 1.07] | 0.303 |
| National origin  (Non-Dutch) *2* | 0.88 | [0.73, 1.06] | 0.185 |
| Urbanicity of living environment (Rural)*2* | 1.19 | [1.00, 1.42] | 0.054 |
| Urbanicity of living environment (Suburban) | 1.07 | [0.88, 1.30] | 0.488 |
| Household income (€1600 – 2399)*2* | 1.07 | [0.82, 1.39] | 0.628 |
| Household income (€2400 – 4399) | 0.94 | [0.75, 1.19] | 0.617 |
| Household income (>€4400) | 0.87 | [0.67, 1.14] | 0.321 |
| Parental BSI score | 1.15 | [0.77, 1.71] | 0.500 |
| Parental drug use | 1.41 | [1.00, 1.99] | 0.050 |
| *1*Reference category for earliest adverse life events dummy variable is “Never experienced an adverse life event” | | | |
| *2*Reference category for sex is “male”; for national origin “Dutch”; for urbanicity of living environment “urban”; for SES “<€1600” | | | |

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| Appendix Table 5. Incidence rate ratio (IRR) Poisson coefficient estimates from sensitivity analysis model. Count of physical adverse life events (ALE) consisting of physical or sexual abuse were coded as occurring either in the past two years or earlier to assess the effect of abuse recency | | | |
|  | **IRR** | **95% CI** | **p-value** |
| Physical ALE earlier than past two years | 1.06 | [0.38, 1.35] | 0.448 |
| Physical ALE in the past two years | 1.39 | [0.99, 1.68] | 0.002 |
| Age | 1.38 | [1.27, 1.50] | < .001 |
| Sex (Female) *1* | 0.94 | [0.82, 1.09] | 0.349 |
| National origin  (Non-Dutch) *1* | 0.87 | [0.73, 1.05] | 0.106 |
| Urbanicity of living environment (Rural) *1* | 1.17 | [0..98, 1.39] | 0.070 |
| Urbanicity of living environment (Suburban) | 1.03 | [0.85, 1.25] | 0.598 |
| Household income (€1600 – 2399) *1* | 1.13 | [0.85, 1.49] | 0.439 |
| Household income (€2400 – 4399) | 1.00 | [0.79, 1.28] | 0.970 |
| Household income (>€4400) | 0.91 | [0.69, 1.22] | 0.513 |
| Parental BSI score | 1.20 | [0.80, 1.81] | 0.324 |
| Parental drug use | 1.39 | [0.97, 2.00] | 0.100 |
| *1*Reference category for sex is “male”; for national origin “Dutch”; for urbanicity of living environment “urban”; for SES “<€1600” | | | |

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| Appendix Table 6. Odds ratio (ORR) ordered logistic regression coefficient estimates from modelling the effect of physical adverse life events (ALE; consisting of sexual and physical abuse) on frequency of alcohol, tobacco and marijuana use | | | | | | | | | |
|  | **Alcohol use** | | | **Tobacco use** | | | **Marijuana use** | | |
| **OR** | **95% CI** | **p-value** | **OR** | **95% CI** | **p-value** | **OR** | **95% CI** | **p-value** |
| Physical ALE before 3*1* | -1.86 | [-3.76, -0.50] | 0.019 | -0.02 | [-1.91, 1.35] | 0.983 | -0.61 | [-3.58, 1.16] | 0.577 |
| Physical ALE 4 To 8 | 0.39 | [-0.19, 0.96] | 0.182 | 0.46 | [-0.33, 1.17] | 0.222 | 0.86 | [ 0.03, 1.62] | 0.032 |
| Physical ALE 9 To 12 | -0.03 | [-0.50, 0.44] | 0.906 | 0.13 | [-0.58, 0.76] | 0.704 | -0.02 | [-0.90, 0.75] | 0.962 |
| Physical ALE Older Than 12 | 0.37 | [-0.15, 0.88] | 0.164 | 0.33 | [-0.39, 0.99] | 0.339 | 0.67 | [-0.08, 1.36] | 0.065 |
| Age | 0.55 | [ 0.36, 0.75] | < .001 | 0.25 | [-0.01, 0.51] | 0.063 | 0.80 | [ 0.49, 1.12] | < .001 |
| Sex (Female) *2* | 0.02 | [-0.26, 0.31] | 0.863 | 0.27 | [-0.14, 0.69] | 0.2 | -0.29 | [-0.79, 0.20] | 0.252 |
| National origin  (Non-Dutch) | 0.40 | [ 0.05, 0.75] | 0.024 | 0.47 | [-0.01, 0.94] | 0.051 | 0.32 | [-0.27, 0.89] | 0.278 |
| Urbanicity of living environment (Rural) *2* | 0.13 | [-0.24, 0.50] | 0.486 | -0.16 | [-0.77, 0.40] | 0.583 | -0.08 | [-0.81, 0.58] | 0.826 |
| Urbanicity of living environment (Suburban) | 0.54 | [ 0.00, 1.09] | 0.053 | 0.25 | [-0.51, 1.05] | 0.521 | -0.13 | [-1.00, 0.74] | 0.764 |
| Household income (€1600 – 2399) *2* | 0.22 | [-0.26, 0.71] | 0.365 | -0.02 | [-0.69, 0.71] | 0.963 | -0.24 | [-0.96, 0.54] | 0.537 |
| Household income (€2400 – 4399) | 0.05 | [-0.49, 0.59] | 0.866 | 0.06 | [-0.69, 0.85] | 0.871 | -0.57 | [-1.46, 0.33] | 0.21 |
| Household income (>€4400) | -0.21 | [-0.57, 0.15] | 0.258 | -0.16 | [-0.69, 0.35] | 0.558 | -0.04 | [-0.66, 0.55] | 0.908 |
| Parental BSI score | 0.56 | [-0.21, 1.34] | 0.152 | -0.05 | [-1.20, 0.99] | 0.925 | -0.13 | [-1.51, 1.10] | 0.846 |
| Parental drug use | 0.62 | [-0.14, 1.37] | 0.109 | 0.75 | [-0.30, 1.67] | 0.128 | 1.09 | [ 0.02, 2.04] | 0.031 |
| *1*Reference category for physical ALE in this analysis is “Never experienced a life event” | | | | | | | | | |
| *2*Reference category for sex is “male”; for national origin “Dutch”; for urbanicity of living environment “urban”; for SES “<€1600” | | | | | | | | | |

Appendix Figure 3. Estimated probabilities for substance use frequency responses (marijuana and alcohol) according to how many physical adverse life events have occurred in each age period. Presented in color age periods with significant effects on use frequency.