Under the skin

Early-life stress exposure and the co-occurrence of mental and physical health problems

Table of contents

# PREFACE

*“In the depth of winter, I found there was, within me, an invincible summer.”* Albert Camus – Summer (1954)

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| --- | --- |
|  | This is a work in progress. Stay tuned :) |

## Aknowledgements

TODO

# INTRODUCTION

Dear reader,

oh my good why does this not update

This an that (Fraser et al., 2013; R Core Team, 2021)

See [Chapter 1](#sec-chapter1) for additional discussion.

## References

Fraser, A., Macdonald-Wallis, C., Tilling, K., Boyd, A., Golding, J., Davey Smith, G., Henderson, J., Macleod, J., Molloy, L., Ness, A., Ring, S., Nelson, S. M., & Lawlor, D. A. (2013). Cohort profile: The avon longitudinal study of parents and children: ALSPAC mothers cohort [Journal Article]. *Int J Epidemiol*, *42*(1), 97–110. <https://doi.org/10.1093/ije/dys066>

R Core Team. (2021). *R: A language and environment for statistical computing* [Journal Article]. <https://www.R-project.org/>

# 1. ELS and adolescent psycho-physical health

Adapted from:

**Differential effects of pre- and postnatal early-life stress on internalizing, adiposity and their comorbidity**

**Defina, S.**, Woofenden, T., Baltramonaityte, V., Pariante, C. M., Lekadir, K., Jaddoe, V. W., Serdarevic, F., Tiemeier, H., Walton, E., Felix, J. F., & Cecil, C. A. M., \*on behalf of the EarlyCause Consortium. (2023). *JAACAP*. [DOI](https://doi.org/10.1016/j.jaac.2023.05.034)

## Abstract

Objective: Depression and obesity are two highly prevalent and often comorbid conditions. Exposure to early-life stress (ELS) has been associated with both depression and obesity in adulthood, as well as their preclinical manifestations during development. However, it remains unclear whether: *(i)* associations differ depending on the timing of stress exposure (prenatal vs postnatal) and *(ii)* ELS is a shared risk factor underlying the comorbidity between the two conditions.

Method: Leveraging data from two large population-based birth cohorts (ALSPAC: n=8428 (52% male participants); Generation R: n=4268 (48% male participants)), we constructed comprehensive cumulative measures of prenatal (in utero) and postnatal (from birth to 10 years) ELS. At age 13.5 years we assessed: a) internalizing symptoms (using maternal reports); b) fat mass percentage (using dual-energy X-ray absorptiometry); c) their comorbidity, defined as the co-occurrence of high internalizing and high adiposity.

Results: Both prenatal (*total effect* [95%CI] = 0.20 [0.16; 0.22]) and postnatal stress ( [95%CI] = 0.22 [0.17; 0.25]) were associated with higher internalizing symptoms, with evidence of a more prominent role of postnatal stress. A weaker association (primarily driven by prenatal stress) was observed between stress and adiposity (prenatal: 0.07 [0.05; 0.09]; postnatal: 0.04 [0.01; 0.07]). Both pre- (OR [95%CI] = 1.70 [1.47; 1.97]) and postnatal stress (1.87 [1.61; 2.17]) were associated with an increased risk of developing comorbidity.

Conclusion: We found evidence of *(i)* timing and *(ii)* shared causal effects of ELS on psycho-cardiometabolic health in adolescence, but future research is warranted to clarify how these associations may unfold over time.

## 1.1 Introduction

In summary, this book has no content whatsoever (Elsenburg et al., 2017; Wiklund et al., 2008). But I shall write it anyway cause. Cause I kind of do have no choice so, checking justification works

## 1.2 Methods

## 1.3 Results

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| Table 1.1: My interesting caption.   | **Sample descriptives** Generation R (GenR) and ALSPAC cohorts | | | | --- | --- | --- | |  | **GenR** **(*n* = 4268)** | **ALSPAC** **(*n* = 8428)** | | **Prenatal stress**, median (range) | | | | Total score | 0.42 (0–2.60) | 0.48 (0–2.34) | | Life events | 0.13 (0–0.67) | 0.07 (0–0.57) | | Contextual risk | 0.25 (0–1.00) | 0.25 (0–0.88) | | Parental risk | 0.00 (0–0.71) | 0.10 (0–0.83) | | Interpersonal risk | 0.06 (0–0.95) | 0.00 (0–0.84) | | **Postnatal stress**, median (range) | | | | Total score | 0.64 (0–3.59) | 2.69 (0.17–16.43) | | Life events | 0.23 (0–0.82) | 1.07 (0–3.50) | | Contextual risk | 0.20 (0–1.00) | 0.50 (0–2.90) | | Parental risk | 0.00 (0–0.79) | 0.57 (0–3.62) | | Interpersonal risk | 0.00 (0–0.79) | 0.29 (0–5.49) | | Direct victimization | 0.13 (0–0.86) | 0.00 (0–3.10) | | **Internalizing score**, median (range) | 4.00 (0–41) | 1.00 (0–10) | | **Fat mass percentage**, median (range) | 24.7 (8.5–54.6) | 23.9 (4.9–56.3) | | **Outcome groups**, n (%) | | | | Healthy | 2791 (65) | 5916 (70) | | High internalizing | 623 (15) | 795 (9) | | High adiposity | 631 (15) | 1476 (18) | | Comorbid | 223 (5) | 241 (3) | | **Sex**, n (%) | | | | Male participants | 2087 (48) | 4370 (52) | | Female participants | 2181 (52) | 4058 (48) | | **Ethnic background**, n (%) | | | | Africa and Middle East a | 115 (2.7) |  | | Asia and Oceania a | 100 (2.3) | | Cape Verdean | 100 (2.3) | | Dutch | 2673 (62.6) | | Dutch Antillean | 118 (2.8) | | Europe a | 334 (7.8) | | Latin America a | 72 (1.7) | | Moroccan | 176 (4.1) | | North America a | 25 (0.6) | | Surinamese | 296 (6.9) | | Turkish | 247 (5.8) | | **Age of the child**, median (range), years | 13.5 (12.6–16.6) | 13.5 (12.8–15.0) | | **Pre-pregnancy** **BMI**, median (range), kg/m2 | 22.6 (14.4–50.2) | 22.1 (12.5–48.6) | | **Maternal smoking**, n (%) | | | | Never | 3228 (76) | 4412 (52) | | Until (early) pregnancy | 390 (9) | 2524 (30) | | During pregnancy | 650 (15) | 1492 (18) | | **Maternal alcohol consumption**, GenR: n (%); ALSPAC: median (range) | | | | Never | 1694 (40) | 0.50 (0 – 3.5) | | Until early pregnancy | 596 (14) | | Continued occasionally | 1570 (37) | | Continued frequently | 407 (10) | | **Maternal education**, n (%) b | | | | Low | 1716 (40.2) | 4216 (50.0) | | Medium | 1278 (29.9) | 3001 (35.6) | | High | 1274 (29.9) | 1212 (14.4) | | **Household income**, n (%) c | | | | Low | 702 (16.4) | 1318 (15.6) | | Medium | 2070 (48.5) | 4324 (51.3) | | High | 1497 (35.1) | 2786 (33.1) | | Note: Sample descriptives pooled across 30 imputed datasets. BMI = Body-mass index. | | | | a **Ethnic backgroung grouping**: Africa and Middle East = Iran (n=11); Iraq (10); South Africa (8); Angola (7); Eritrea (7); Israel (6); Cameroon (5); Egypt (5); Nigeria (5); Ethiopia (4); Algeria (3); Ghana (3); Lebanon (3); Liberia (3); Syria (3); Tanzania (3); Côte d'Ivoire (2); Guinea (2); Mozambique (2); Saudi Arabia (2); Senegal (2); Zimbabwe (2); Africa (1); Armenia (1); Burundi (1); Congo (1); French Congo (1); Gambia (1); Kenya (1); Mali (1); Mauritania (1); Palestine (1); Sierra Leone (1); Somalia (1); Sudan (1); Togo (1); Tunisia (1); Uganda (1); Yemen (1). Asia and Oceania = Indonesia (n=23); Pakistan (9); Australia (6); China (6); Japan (6); Philippines (6); Thailand (6); India (5); Afghanistan (4); Hongkong (4); South Korea (4); Vietnam (4); Bangladesh (3); Korea (3); Taiwan (3); Kazakhstan (2); New Zealand (2); Dutch New Guinea (1); East Timor (1); Singapore (1); Sri Lanka (1). Europe = Germany (n=55); Belgium (35); United Kingdom (30); France (29); Portugal (22); Spain (18); Yugoslavia (18); Poland (16); Italy (12); Bosnia-Herzegovina (11); Russia (10); Croatia (7); Czech Republic (7); Switzerland (7); Hungary (6); North Macedonia (6); Serbia-Montenegro (5); Denmark (4); Ireland (4); Norway (4); Sweden (4); Greece (3); Lithuania (3); Romania (3); Austria (2); Kosovo (2); Ukraine (2); Canary Islands (1); Estonia (1); Finland (1); Luxembourg (1); Madeira Islands (1); Moldova (1); Monaco (1); Slovakia (1); Slovenia (1). Latin America = Colombia (n=18); Brazil (11); Dominican Republic (8); Chile (6); Venezuela (6); Cuba (4); Mexico (4); Argentina (3); Peru (3); Ecuador (2); Guyana (2); Belize (1); Bolivia (1); Haiti (1); Paraguay (1); Trinidad and Tobago (1). North America = United States of America (n=16); Canada (9). | | | | b **Maternal education**: low = “secondary, phase 2” or lower in GenR, “None”, “CSE”, “Vocational” or “O level” in ALSPAC; medium = “higher, phase 1” in GenR, “A level” in ALSPAC; high = “higher, phase 2” in GenR, “(College or university) degree” in ALSPAC. Categorization based on ISCED 2011. | | | | c **Household income**: low = < €1600 /month in GenR, < £200 /week in ALSPAC; medium = between €1600 and € 4000 /month in GenR, between £200 and £400 /week in ALSPAC; high = > € 4000 /month in GenR, > £400 /week in ALSPAC. | | | |

See [Table 1.1](#tbl-table1.1) for desctiptives.

## 1.4 Discussion

## References

Elsenburg, L. K., Wijk, K. J. E. van, Liefbroer, A. C., & Smidt, N. (2017). Accumulation of adverse childhood events and overweight in children: A systematic review and meta-analysis [Journal Article]. *Obesity (Silver Spring)*, *25*(5), 820–832. <https://doi.org/10.1002/oby.21797>

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# 2. Lifestyle factors, ELS and adolescent psycho-physical health

Adapted from:

The role of lifestyle factors in the association between early-life stress and adolescent psycho-physical health: Moderation analysis in two European birth cohorts

**Defina, S.**, Woofenden, T., Baltramonaityte, V., Tiemeier, H., Fairchild, G., Felix, J. F., Cecil, C.A.M., & Walton, E. (2024). *Preventive Medicine*. [DOI](https://doi.org/10.1016/j.ypmed.2024.107926)

## Abstact

## 2.1 Introduction

In summary, this book has no content whatsoever (Boyd et al., 2012; Fraser et al., 2013). But I shall write it anyway cause. Cause I kind of do have no choice so, checking justification works

## 2.2 Methods

## 2.3 Discussion

## References

## References

Boyd, A., Golding, J., Macleod, J., Lawlor, D. A., Fraser, A., Henderson, J., Molloy, L., Ness, A., Ring, S., & Davey Smith, G. (2012). Cohort profile: The ’children of the 90s’—the index offspring of the avon longitudinal study of parents and children [Journal Article]. *International Journal of Epidemiology*, *42*(1), 111–127. <https://doi.org/10.1093/ije/dys064>

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# 3. ELS and intracortical myelination

Adapted from:

Early-life stress exposure and intracortical myelination in childhood: a population-based neuroimaging study

**Defina, S.**, Manzoni, D., Tiemeier, H., Brouwer, R.M., Cecil, C.A.M., & Muetzel R.L. (*in preparation*)

## Abstact

## 3.1 Introduction

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## 3.2 Methods

## 3.3 Discussion

## References

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# 4. ELS and cardiac morphology

Adapted from:

Early-life stress exposure and heart morphology in childhood: a prospective population-based study

**Defina, S.**, Kamphuis, A., Gaillard, R., & Felix, J. F. (*in preparation*)

## Abstact

## 4.1 Introduction

In summary, this book has no content whatsoever (Boyd et al., 2012; Fraser et al., 2013). But I shall write it anyway cause. Cause I kind of do have no choice so, checking justification works

## 4.2 Methods

## 4.3 Discussion

## References

## References

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# 5. Longitudinal psycho-physical co-development

Adapted from:

Longitudinal co-development of depressive symptoms and cardio-metabolic risk factors from childhood to young adulthood

Defina, S., Cecil, C.A.M., Felix, J.F., Walton, E., & Tiemeier, H. (*under revision*)

## Abstact

## 5.1 Introduction

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## 5.2 Methods

## 5.3 Discussion

## References

## References

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# DISCUSSION

See [Chapter 1](#sec-chapter1) for whatever whatever.

## References

# References

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Wiklund, P., Toss, F., Weinehall, L., Hallmans, G., Franks, P. W., Nordstrom, A., & Nordstrom, P. (2008). Abdominal and gynoid fat mass are associated with cardiovascular risk factors in men and women [Journal Article]. *The Journal of Clinical Endocrinology & Metabolism*, *93*(11), 4360–4366.