NOVEL ANALYTICAL STRATEGIES FOR LONGITUDINAL STUDIES: WHICH MODEL TO CHOOSE?

Prof Dr A. Burdorf
Department of Public Health
Erasmus MC Rotterdam, Netherlands

Erasmus MC

The problem and the debate

Essay Review

Causal inference—so much more than statistics

Neil Pearce[1,2*] and Debbie A Lawlor[3,4]

International Journal of Epidemiology, 2016, 1895–1903

Causality and causal inference in epidemiology: the need for a pluralistic approach

Jan P Vandenbroucke,[1,*,†] Alex Broadbent[2,†] and Neil Pearce[3]

International Journal of Epidemiology, 2016, 1776–1786

Causality and study design:

'interventionists' versus 'observationalists'

Discussion paper
Scand J Work Environ Health 2015;41(5):491-503
doi:10.5271/sjweh.3505

Evaluation of occupational health interventions using a randomized controlled trial: challenges and alternative research designs

by Schelvis RMC, Oude Hengel KM, Burdorf A, Blatter BM, Strijk JE, van der Beek AJ

Novel analytical strategies in observational studies: the holy grail

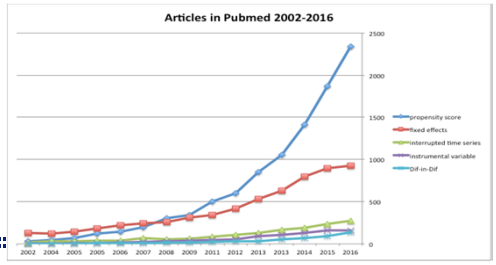
The search for 'exchangeability' in observational studies, whereby the condition of interest (e.g. exposure, intervention) will not be determined by characteristics of the study population, hence, groups with and without the condition of interest are comparable for measured and unmeasured variables

- natural experiments whereby the assignment process of individuals to comparison groups resembles random variation in assignment (reality as random process)

Classical example: introduction of interventions at a specific point in time (e.g. legislation)

Erasmus MC

Novel analytical strategies in recent years



Erasmus MC

Why this increase in popularity of Fixed Effects models ?

- focus on the influence of changes in exposure within individuals on outcome measures, whereby individual characteristics cannot create selection bias
  (by definition)
  (cf case-crossover design)
- easy to implement in existing analytical models
  (a simple analysis of change)

Erasmus MC

My first Fixed Effects model

Why Fixed Effects model:

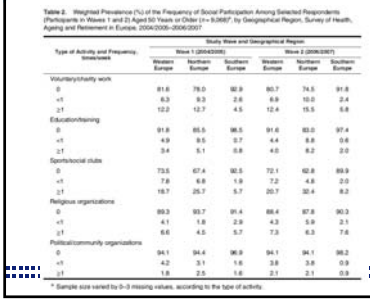
- risk of bias: persons with particular traits may be more likely to engage in social activities, and may also exhibit lower levels of depressive symptoms
- within-person estimators will control for unobserved individual heterogeneity that may be correlated with determinant of interest
- societal context may be important


Original Contribution

Social Participation and Depression in Old Age: A Fixed-Effects Analysis in 10 European Countries

Simone Croezen, Maurizio Avendano, Alex Burdorf, and Frank J. van Lenthe*

My first Fixed Effects model



Categories:
0 = less than once per month
1 = almost every month
2 = almost every week
3 = almost every day

My first Fixed Effects model

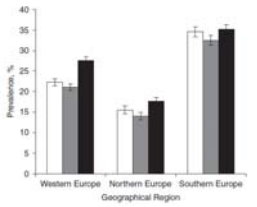


Figure 1. Weighted estimates of the prevalence (%) of ≥4 depressive symptoms among respondents aged 50 years or older, by geographical region, in waves 1 (n = 9,027), 2 (n = 9,068), and 4 (n = 9,068) of the Survey of Health, Ageing and Retirement in Europe, 2004–2011. White columns represent wave 1 (2004/2005), gray columns represent wave 2 (2006/2007), and black columns represent wave 4 (2010/2011). T-shaped bars, standard errors.

Categories:
0 = less than once per month
1 = almost every month
2 = almost every week
3 = almost every day

My first Fixed Effects model

Table 3. Four-Year-Lagged Associations Between Changes in Social Participation and Changes in Depressive Symptom Score Among Selected Respondents (Participants in Waves 1, 2, and 4) Aged 50 Years or Older, Survey of Health, Ageing and Retirement in Europe, 2004/2005–2010/2011

Type of Activity	Model 1[a] (n = 9,068)		Model 2[b] (n = 7,385)	
	β	Robust 95% CI	β	Robust 95% CI
Voluntary/charity work	0.085	−0.022, 0.193	0.020	−0.112, 0.152
Education/training	0.023	−0.096, 0.141	0.041	−0.101, 0.183
Sports/social clubs	0.097	0.004, 0.190	0.081	−0.036, 0.199
Religious organizations	−0.145	−0.281, −0.010	−0.190	−0.365, −0.016
Political/community organizations	0.111	−0.051, 0.273	0.222	0.018, 0.428

Abbreviation: CI, confidence interval.
[a] Results were adjusted for social participation (mutually adjusted), age, and time.
[b] Results were adjusted for social participation (mutually adjusted), age, time, household size, marital status, employment status, financial difficulties, self-rated health, long-term illness, activity limitations, and physician-diagnosed diseases (heart attack, high blood pressure or hypertension, stroke, diabetes or high blood sugar, and chronic lung disease).

My first Fixed Effects model

The popularity of the article:

- citations in scientific literature: 26 (about 8 per year)
- media cites: > 200 in one week

If you want to be cheerful … go to church

The Times, 05/08/2015

Church-going helps to keep depression at bay for elderly

Daily Telegraph

Kirkegang er nøglen til godt psykisk helbred

Et religiøst fællesskab har en positiv effekt på folk over 50 år, viser europæisk undersøgelse

Kristeligt Dagblad.dk

Una mano dal cielo: andare in chiesa è un antidepressivo

Pubblicato il: 08/08/2015 15:04

Three models for analysis in longitudinal studies

Which model should we use?

- Random effect model
- Fixed effects model
- Hybrid (combination random and fixed effects) model

Note:
Example whereby an RCT is hard to conduct
(intervention = entering paid employment) !

Study population and design

Longitudinal data with 2 years follow up
(up to three repeated measurements of independent *and* dependent variables)
Study population: 749 welfare-recipients, 1792 observations

Independent variables:
- employment status
- sociodemographic characteristics

Dependent variables:
- mental and physical health
- mastery and self-esteem
- happiness

Scand J Work Environ Health 2017;43(6):540-549
doi:10.5271/sjweh.3675

The benefits of paid employment among persons with common mental health problems: evidence for the selection and causation mechanism
by Schuring M, Robroek SJW, Burdorf A

Random effect model (also called mixed model)

The individual-specific intercept (β_{0i}) is a random factor
Measured time-varying and time-constant factors can be included in the model

Regression equation: $Y=\beta_{0i}+\beta_1 x + \ldots$.
β_{0i} = random intercept (hence, the name random model)
β_1 = association between paid employment (x) and health (Y)

Interpretation
Insight in health difference between employed and unemployed persons
Not possible to distinguish between persons who were already employed and persons who became employed during follow-up

Random effect model (also called mixed model)

Descriptive information of longitudinal study

Table 2. Mental health, physical health, mastery, self-esteem, and happiness among persons with common mental health problems who are unemployed or employed for ≥12 hours per week, at baseline and after 1 and respectively 2 years of follow-up. [SD=standard deviation].

	Baseline						After 1 year						After 2 years					
	Employed N=9			Unemployed N=740			Employed N=48			Unemployed N=538			Employed N=42			Unemployed N=421		
	Mean	SD	%	Mean	SD	%	Mean	SD	%	Mean	SD	%	Mean	SD	%	Mean	SD	%
Mental health (0–100, higher is better)	54.9	29.5		39.2	23.9		63.9	25.4		43.2	24.9		65.4	25.1		44.8	24.1	
Physical health (0–100, higher is better)	61.9	10.9		51.2	27.8		66.5	27.8		50.9	27.4		69.5	24.2		54.1	27.3	
Self esteem (10–40, higher is better)	28.6	6.3		26.8	4.7		31.8	4.0		26.9	5.1		32.7	5.1		27.2	5.4	
Mastery (6–18, higher is better)	11.3	2.1		10.8	2.9		13.6	2.9		11.2	3.2		14.2	3.2		11.1	3.38	
Happiness (happy/very happy)			28.6			35.7			67.4			41.4			66.7			37.6

Random effect model (also called mixed model)

The effect of paid employment on health

	Random effect on health (Δ)	Baseline unemployed persons
Mental health	18.41 ± 2.53	39.2 ± 23.9
Physical health	10.67 ± 2.42	51.2 ± 27.8

Random effect model (also called mixed model)

Principles:
1. Variables and confounders as time-varying or time-independent factors
2. Repeated measurements for a substantial part of persons

Disadvantages:
1. Heterogeneity between individuals is assumed a random variable with zero mean with a constant variance (not always realistic assumption)
2. Random variable for heterogeneity between individuals is independent from (unmeasured) confounders
3. The estimates combines within and between variation (i.e. difference between persons with and without a specific condition AND persons who change from without to with condition or vice versa)

Fixed effects model

Solution for problems of random model: person as his/her own control
(e.g. case-crossover design, fixed effects model)

Principles:
1. Different treatment statuses within the same individual: a person as own control
2. Control for all known and unknown attributes of subjects (time invariant; fixed)
3. Time-varying factors can be included in the model

Requirements:
1. The outcome variable must be measured at least twice for each individual
2. The treatment status must change across two measurements for a substantial proportion of the study population

When applicable ?

(mean centered) Fixed effects model

Group-mean centering of time-varying factors:
Subtraction of the individual mean value from each observation (=deviation score)
Applied for both the independent (time-varying) variables as well as dependent variable
Note: With two measurements: first difference model

Core regression equation $y_{it}-y_i = \beta_W(x_{it}- x_i) + \varepsilon_{it}$
β_W = association between change in employment (x) and change in health (y)

(mean centered) Fixed effects model

Complete FE model:

$y_{it}-y_i = \beta_{0t} + \beta_W(Factor_{it}) + \beta_2(x_{it}- x_i) + \mu_i + \varepsilon_{it}$

β_{0t} = intercept, that my be different for each point in time
β_W = Factor = Paid employment = association between change in employment (x) and change in health (y)
$\beta_2(x_{it}- x_i)$ = time-varying covariates
μ_i = error term for time-invariant covariates (whether observed or not) for individual *i*, presented as a fixed intercept for each individual
ε_{it} = random error for individual *i* at time *t*

(mean centered) Fixed effects model

Different FE models:

1. Regress change in exposure between wave 1 and wave 2 on change in health between wave 1 and wave 2 (contemporaneous association)

2. Regress change in exposure between wave 1 and wave 2 on change in health between wave 2 and wave 3 (lagged association)

(mean centered) Fixed effects model

Comparision of effect of paid employment on health

	Random effect on health (Δ)	Fixed effects (within)
Mental health	18.41 ± 2.53	16.47 ± 2.78
Physical health	10.67 ± 2.42	9.86 ± 2.69

Comparison:
- confidence intervals higher in FE model

Theory on why results are similar ?

Fixed effects model

Interpretation:
* Insight in changes in health within individuals who enter of exit paid employment
* Exposure-response relationship: estimate is a population average effect
* change in exposure as exogenous variable; truly exogenous ?
* high internal validity, low external validity

Disadvantage:
* Not possible to estimate time-invariant variables in the model (random term)
* No information on context (i.e. individual characteristics, eg education, sex)
* Power considerations:
  * persons without a change in the independent variable contribute only a little
  * logistic regression model: persons without a change in dependent variable are not included in the analysis

Hybrid model (combine random and mixed effects model)

Group-mean centering of time-varying independent factors:
Subtraction of the individual mean value from each observation

Additionally included in the model:
Individual mean values of time-varying factors (x)
Time-constant factors (z)
Random individual-specific intercept (β_{0i})

Regression equation $y_{it} = \alpha_t + \beta_{0i} + \beta_W(x_{it}- x_i) + \beta_B x_i + \mu_i + \varepsilon_{it}$

Interpretation
Insight in changes in health within (β_W) as well as differences between (β_B) individuals
Estimates are not biased by unmeasured time-constant factors

Hybrid model

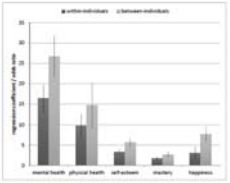


Figure 2. Within-individual (change from unemployment to employment) and between-individual (unemployed versus employed persons) associations of employment status and health- and psychological measures among persons with common mental health problems (N=749).

Overall results of hybrid model

Hybrid model

	within-individual change β (SD)	between-individuals difference β (SD)
Mental health (0-100, higher is better)	16.34 (3.40)	26.74 (5.08)
Physical health (0-100, higher is better)	9.79 (2.86)	14.61 (5.57)
Self esteem (0-100, higher is better)	11.23 (2.21)	19.00 (3.56)
Mastery (0-100, higher is better)	14.11 (3.18)	22.81 (5.35)
	OR (95%CI)	OR (95%CI)
Happiness (happy/very happy)	3.08 (1.37-6.93)	7.74 (2.27-26.36)

Entering paid employment has a positive influence on mental and physical health, self esteem, mastery and happiness

Comparison of three models

Comparision of effect of paid employment on health

	Random effect on health (Δ)	Fixed effects (within)	Hybrid model (within)	(between)
Mental health	18.41 ± 2.53	16.47 ± 2.78	16.34 ± 3.40	26.74 ± 5.08
Physical health	10.67 ± 2.42	9.86 ± 2.69	9.79 ± 2.86	14.61 ± 5.57

Comparison:

- confidence intervals higher in FE model, highest in hybrid model

Comparison of three models

	Random	Fixed	Hybrid
Variables included in the model			
- Only time-varying variables		X	
- Time-varying & time-constant variables	X		X
Persons included in the analysis			
- Only persons with change of time-varying variable		X	
- All persons (with or without change of x in time)	X		X
Not biased by unmeasured time-constant variables		X	X
Estimates for changes within individuals		X	X
Estimates for differences between individuals			X

Fixed effects model - revisited

Criticism on fixed effects model:

1. No information on context (eg education, gender); important factors of between-individual variation
2. Independent factor is defined by a sudden change and, thus, fixed effects model cannot by used to study long-term consequences or cumulative exposure
   (e.g. effect of smoking on lung cancer cannot be studied with FE model)
3. Change is estimated as combined effect (0 to 1 and 1 to 0)
4. Dependent variable must be measured twice, thus, this limits topics to be studied, eg no mortality as endpoint!
   (Alternative strategy: case-crossover design)

Fixed effects model – illustrative example

Table 4. Association of within-person changes in psychosocial job quality and time-varying covariates with changes in mental health score. Fixed-effects regression analyses based on 10 534 individuals with 39 761 observations. [95% CI=95% confidence interval]

Time-varying covariates	Unadjusted			Mutually adjusted [a]		
	Coefficient	95 % CI	P-value	Coefficient	95 % CI	P-value
Not in the labor force	0			0		
Psychosocial job quality (number of adversities)						
0	0.74	0.40–1.07	<0.001	0.75	0.40–1.10	<0.001
1	0.19	-0.13–0.51	0.242	0.21	-0.12–0.54	0.219
2	-0.62	-0.98–-0.26	0.001	-0.60	-0.97–-0.23	0.001
≥3	-1.65	-2.15–-1.16	<0.001	-1.68	-2.18–-1.17	<0.001

Significant improvement in mental health when young persons were employed in jobs with good psychosocial working conditions, but significant decline when employed in jobs with poor psychosocial working conditions
Milner et al. Scand J Work Environ Health 2017;43:50-8.

Fixed effects model – illustrative example

Original article

Scand J Work Environ Health Online-first -article

doi:10.5271/sjweh.3730

Association of changes in work shifts and shift intensity with change in fatigue and disturbed sleep: a within-subject study
by Härmä M, Karhula K, Ropponen A, Puttonen S, Koskinen A, Ojajärvi A, Hakola T, Pentti J, Oksanen T, Vahtera J, Kivimäki M

Study design:

- at least two consecutive bi-annual waves (11,949 individuals)
- exposure = shift characteristics, % of work shifts
- health: longer sleep length and fatigue during free days

Fixed effects model – illustrative example

Table 4. The association of working hour characteristics with fatigue during work and free days. Longitudinal fixed-effects model. Odds ratio (OR) refer to every 25% increase in the occurrence of the 3-month prevalence (%) of the continuous exposure variables. Significant interactions according to age and gender. [CI=confidence interval.]

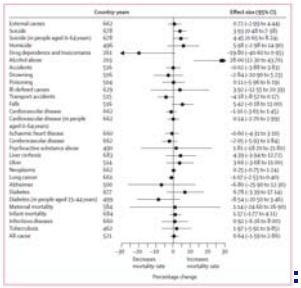
	Fatigue during work				Fatigue during free days			
	N	OR (95% CI)	Age	Gender	N	OR (95% CI)	Age	Gender
Work shifts								
Morning shifts	2059	0.98 (0.88-1.08)	-	-	1753	0.86 (0.78-0.95)	-	-
Evening shifts	2059	1.13 (0.96-1.28)	-	-	1753	1.10 (0.93-1.28)	-	0.092
Night shifts	2059	1.05 (0.90-1.22)	-	-	1753	1.38 (1.16-1.64)	-	0.094
Non-day shifts	2059	1.10 (0.98-1.22)	-	-	1753	1.25 (1.10-1.42)	-	-
Shift Intensity								
Long spells of work shifts	2059	1.10 (0.84-1.42)	-	-	1753	1.25 (0.98-1.64)	-	-
>2 consecutive night shifts	2059	1.10 (1.05-1.19) 1.13 (1.05-1.22)*	-	-	1753	1.10 (1.03-1.18) 1.05 (0.98-1.13)*	-	-
>4 consecutive night shifts	2059	1.05 (0.95-1.13) 1.05 (0.93-1.16)*	-	-	1753	1.00 (0.93-1.10) 1.03 (0.86-1.19)*	-	-
Short shift intervals	2081	1.42 (1.19-1.72)	-	-	1783	1.25 (1.03-1.49)	0.092	-

*Controlled for the % of night shifts.

Exposure: changes in % of shifts

Erasmus MC

Fixed effects model – illustrative example



Analysis:
- FE (ecological) model

Intervention:
- Mass rise in unemployment

Outcome:
- Mortality rates

Stuckler et al . Lancet 2009;374:315-23

Erasmus MC

Fixed effects model – illustrative example

Journal of Public Health | pp. 1–9 | doi:10.1093/pubmed/fdu070

Combining fixed effects and instrumental variable approaches for estimating the effect of psychosocial job quality on mental health: evidence from 13 waves of a nationally representative cohort study

Allison Milner[1,2], Zoe Aitken[1], Anne Kavanagh[1], Anthony D. LaMontagne[2], Frank Pega[3], Dennis Petrie[4]

Erasmus MC

Fixed effects model – illustrative example

Instruments:
1. Workplace entitlement of flexible start and finish times
2. Workplace entitlement of ability to work from home

Rationale on three assumptions:
1. Workplace entitlement (=organizational factor) is likely to be related to psychosocial job quality (exposure at individual level)
2. Workplace entitlement alone will not affect a person's mental health, but its effect acts primarily through psychosocial job quality
3. Workplace entitlement is not associated with unmeasured confounders

Erasmus MC

So, what next ?

1. Popularity of fixed effects models will certainly continue (inching towards causal inference)
2. The classical random effect model (= mixed model) for repeated measurements will most likely remain the most common analytical method
3. Hybrid models have a slow uptake and some debate among statisticians whether we can truly separate within- and between person effects (esp confidence intervals of between person effects are high)

Erasmus MC

Alex Burdorf
Erasmus MC
Department of Public Health
a.burdorf@erasmusmc.nl

Erasmus MC