

Supplementary Material Part 3

Dose-response meta-analyses

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Method description

Calculation of PA exposure levels

Following the procedure of Blond et al (1), we used the midpoint of the physical activity range (mean or median) from each group as the value for PA exposure. MET values for listed activities were taken from the included articles, or estimated using MET values of 3.5 for walking, 4.5 for moderate physical activity and 8.0 for sports participation or vigorous PA. For studies in which PA was assessed as bouts per week, one bout was estimated to be 30 minutes in duration unless otherwise specified in the included article. When physical activity levels were specified in calories per week, mean body weights reported in the articles were used for calculating MET-minutes using the formula

$$MET * minutes = \frac{60 * kcal}{kg}$$

Where mean body weight was not reported in an article, continental body weight averages were used in the calculation (2). In studies where it was not possible to directly calculate MET*minutes per week for each group, we imputed PA exposure values using the means from other similar studies. We used a cutoff of a maximum of 21 hours of moderate PA per week (3 hours X 7 days), and this corresponds to a maximum value of 5040 MET-minutes per week.

Dose-response meta-analyses

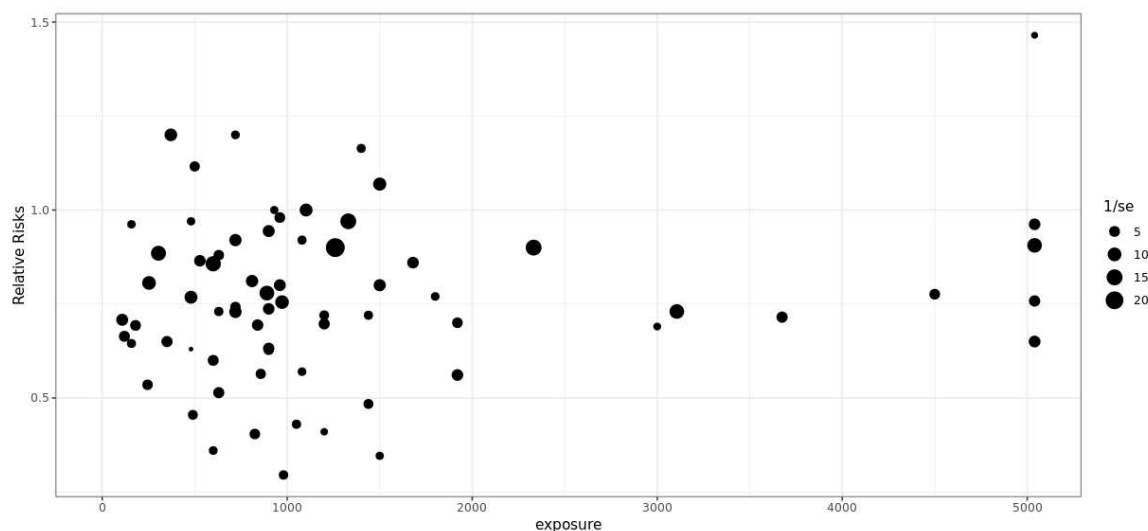
Dose-response meta-analyses were performed using the dosresmeta package (3) in R and visualizations were created using the shiny webapp based on this package (4). Two-stage random effects meta-analyses using the restricted maximum likelihood procedure were used to pool RRs. Among studies with at least 3 different PA exposure levels, dose-response meta-analyses explored linear, quadratic and restricted cubic spline trends within the data. Knots in the restricted cubic spline regression models were set at the 20th and 80th percentiles of the overall PA exposure distribution. As it was not possible to explore quadratic or spline trends among studies with only two different PA exposure levels, we only examined linear trends

within this larger dataset that included all studies with at least two discrete PA exposure groups. We chose 200 MET min/week as the reference for the dose–response analyses as this was roughly equivalent to the mean MET*min per week value of reference groups in the included studies. Post-estimations based on the dose–response model were conducted to predict RRs and 95% CIs at specific MET*min per week values (approximately 200, 900, 2000, 3000, 4000, and 5000).

Results - All-cause dementia (A-CD)

Linear model including all studies (A-CD)

Scatter plot of RRs vs original exposure variable



Linear Trend

```
Call: dosresmeta(formula = logrr ~ exposure, id = id, type = type,
  cases = cases, n = n, data = dataset(), se = se, covariance = input$pscorr)
```

Two-stage random-effects meta-analysis

Estimation method: REML

Covariance approximation: Greenland & Longnecker

Chi2 model: $X^2 = 34.6275$ (df = 1), p-value = 0.0000

Fixed-effects coefficients

	Estimate	Std. Error	z	Pr(> z)	95%ci.lb	95%ci.ub	
(Intercept)	-0.0002	0.0000	-5.8845	0.0000	-0.0003	-0.0001	***

Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Between-study random-effects (co)variance components

Std. Dev

0.0002

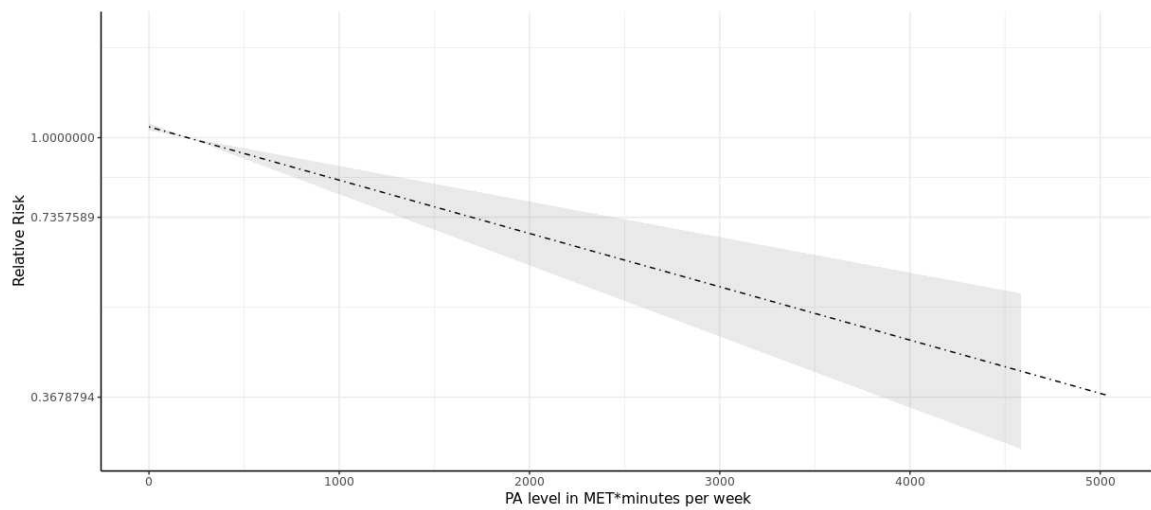
Univariate Cochran Q-test for residual heterogeneity:

Q = 123.3919 (df = 42), p-value = 0.0000

I-square statistic = 66.0%

43 studies, 43 values, 1 fixed and 1 random-effects parameters

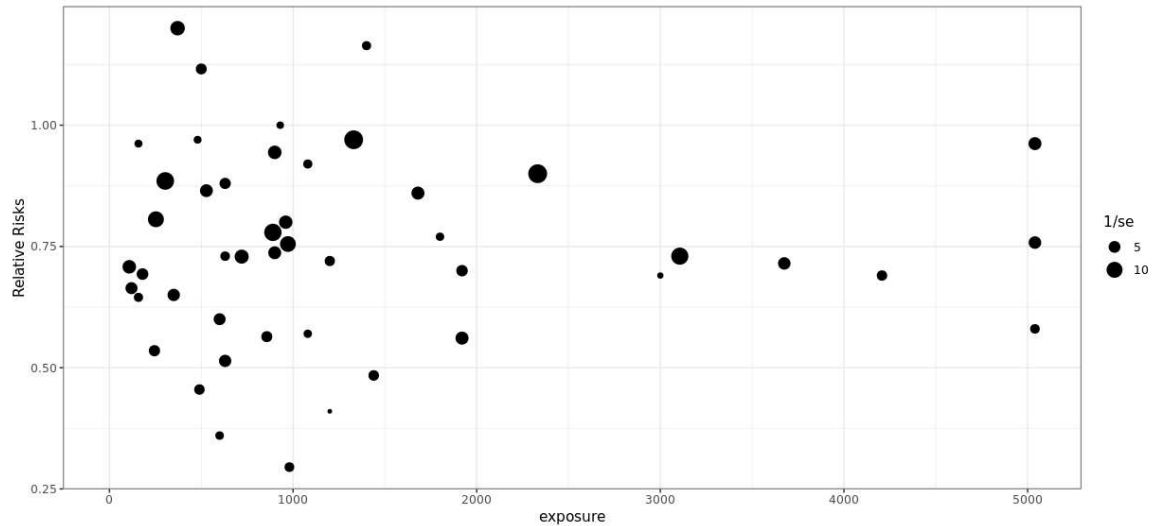
logLik	AIC	BIC
276.7986	-549.5973	-546.1220

Graphical prediction**Analytical predictions**

PA exposure	pred.lin	ci.lb.lin	ci.ub.lin
203.64	1.00	1.00	1.00
916.36	0.86	0.82	0.91
1934.55	0.70	0.62	0.79
2952.73	0.57	0.47	0.69
3970.91	0.46	0.36	0.60
4989.09	0.37	0.27	0.52

Models including studies with 3 or more PA exposure levels (A-CD)

Scatter plot of RRs vs original exposure variable



Linear Trend

```
Call: dosresmeta(formula = logrr ~ exposure, id = id, type = type,
  cases = cases, n = n, data = dataset(), se = se, covariance = input$pscorr)
```

Two-stage random-effects meta-analysis

Estimation method: REML

Covariance approximation: Greenland & Longnecker

Chi2 model: $X^2 = 21.4096$ (df = 1), p-value = 0.0000

Fixed-effects coefficients

	Estimate	Std. Error	z	Pr(> z)	95%ci.lb	95%ci.ub	
(Intercept)	-0.0002	0.0000	-4.6270	0.0000	-0.0003	-0.0001	***

Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Between-study random-effects (co)variance components

Std. Dev

0.0001

Univariate Cochran Q-test for residual heterogeneity:

Q = 57.7815 (df = 19), p-value = 0.0000

I-square statistic = 67.1%

20 studies, 20 values, 1 fixed and 1 random-effects parameters

logLik	AIC	BIC
128.2688	-252.5375	-250.6487

Spline model

Call: dosresmeta(formula = logrr ~ rcs(exposure, knots), id = id, type = type, cases = cases, n = n, data = dataset(), se = se, covariance = input\$pscorr)

Two-stage random-effects meta-analysis

Estimation method: REML

Covariance approximation: Greenland & Longnecker

Chi2 model: X2 = 37.6403 (df = 2), p-value = 0.0000

Fixed-effects coefficients

	Estimate	Std. Error	z	
rcs(exposure, knots)exposure.(Intercept)	-0.0005	0.0001	-5.5896	
rcs(exposure, knots)exposure'.(Intercept)	0.0004	0.0001	4.5834	
	Pr(> z)	95%ci.lb	95%ci.ub	
rcs(exposure, knots)exposure.(Intercept)	0.0000	-0.0006	-0.0003	***
rcs(exposure, knots)exposure'.(Intercept)	0.0000	0.0002	0.0006	***

Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Between-study random-effects (co)variance components

	Std. Dev	Corr
rcs(exposure, knots)exposure	0.0002	rcs(exposure, knots)exposure
rcs(exposure, knots)exposure'	0.0001	-1

Univariate Cochran Q-test for residual heterogeneity:

Q = 58.7637 (df = 38), p-value = 0.0169

I-square statistic = 35.3%

20 studies, 40 values, 2 fixed and 3 random-effects parameters

logLik	AIC	BIC
222.9501	-435.9001	-427.7122

Quadratic trend

```

Call: dosresmeta(formula = logrr ~ exposure + I(exposure^2), id = id,
  type = type, cases = cases, n = n, data = dataset(), se = se,
  covariance = input$pscorr)

Two-stage random-effects meta-analysis
Estimation method: REML
Covariance approximation: Greenland & Longnecker

Chi2 model: X2 = 38.9658 (df = 2), p-value = 0.0000

Fixed-effects coefficients

```

	Estimate	Std. Error	z	Pr(> z)	95%ci.lb
exposure.(Intercept)	-0.0004	0.0001	-4.6303	0.0000	-0.0005
I(exposure^2).(Intercept)	0.0000	0.0000	3.3398	0.0008	0.0000

```

          95%ci.ub
exposure.(Intercept)  -0.0002 ***
I(exposure^2).(Intercept)  0.0000 ***
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Between-study random-effects (co)variance components

```

	Std. Dev	Corr
exposure	0.0002	exposure
I(exposure^2)	0.0000	-1

```

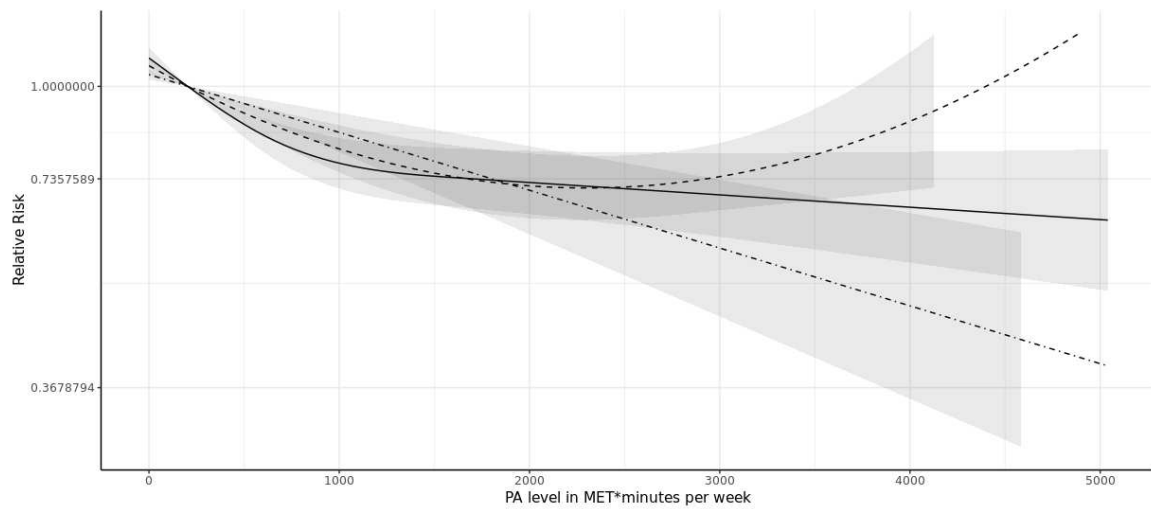
Univariate Cochran Q-test for residual heterogeneity:
Q = 66.0653 (df = 38), p-value = 0.0032
I-square statistic = 42.5%

20 studies, 40 values, 2 fixed and 3 random-effects parameters

```

logLik	AIC	BIC
382.8104	-755.6209	-747.4329

Graphical prediction



Linear Trend (dot-dash); Spline Model with knots at 20 and 80% of distribution (solid); Quadratic Trend (dashed)

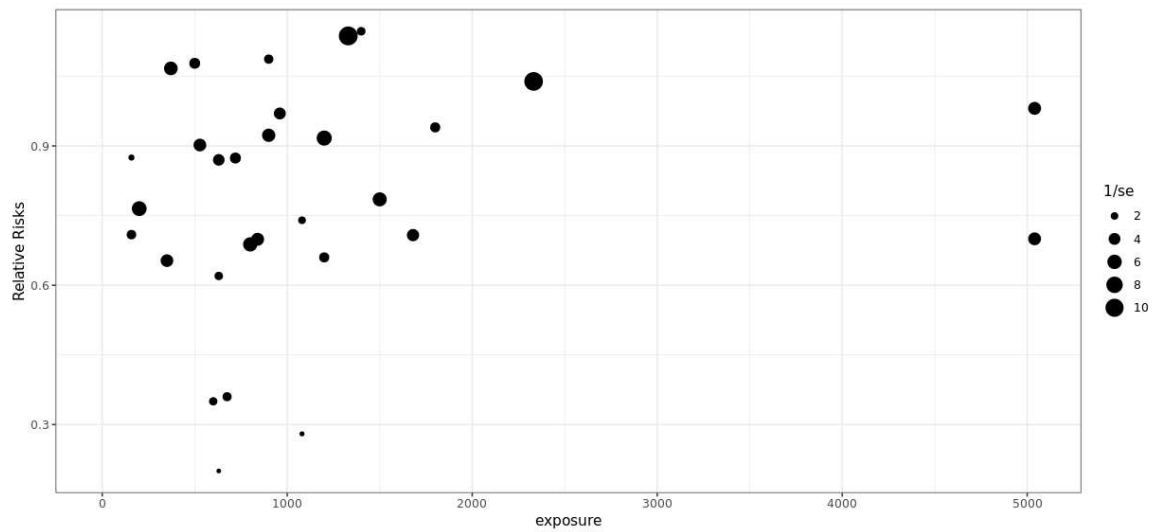
Analytical predictions

exposure	pred.lin	ci.lb.lin	ci.ub.lin	pred.spl	ci.lb.spl	ci.ub.spl	pred.quadr	ci.lb.quadr	ci.ub.quadr
203.64	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
916.36	0.87	0.82	0.92	0.79	0.73	0.85	0.83	0.77	0.89
1934.55	0.72	0.62	0.83	0.73	0.66	0.81	0.72	0.65	0.80
2952.73	0.59	0.47	0.74	0.70	0.61	0.80	0.74	0.66	0.82
3970.91	0.49	0.36	0.66	0.67	0.56	0.80	0.88	0.71	1.11
4989.09	0.40	0.27	0.59	0.64	0.51	0.81	1.24	0.78	1.99

Results - Alzheimer's disease (AD)

Linear model including all studies (AD)

Scatter plot of RRs vs original exposure variable



Linear Trend

```
Call: dosresmeta(formula = logrr ~ exposure, id = id, type = type,
  cases = cases, n = n, data = dataset(), se = se, covariance = input$pscorr)
```

Two-stage random-effects meta-analysis

Estimation method: REML

Covariance approximation: Greenland & Longnecker

Chi2 model: $X^2 = 5.8708$ (df = 1), p-value = 0.0154

Fixed-effects coefficients

	Estimate	Std. Error	z	Pr(> z)	95%ci.lb	95%ci.ub
(Intercept)	-0.0001	0.0000	-2.4230	0.0154	-0.0002	-0.0000 *

Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Between-study random-effects (co)variance components

Std. Dev

0.0001

Univariate Cochran Q-test for residual heterogeneity:

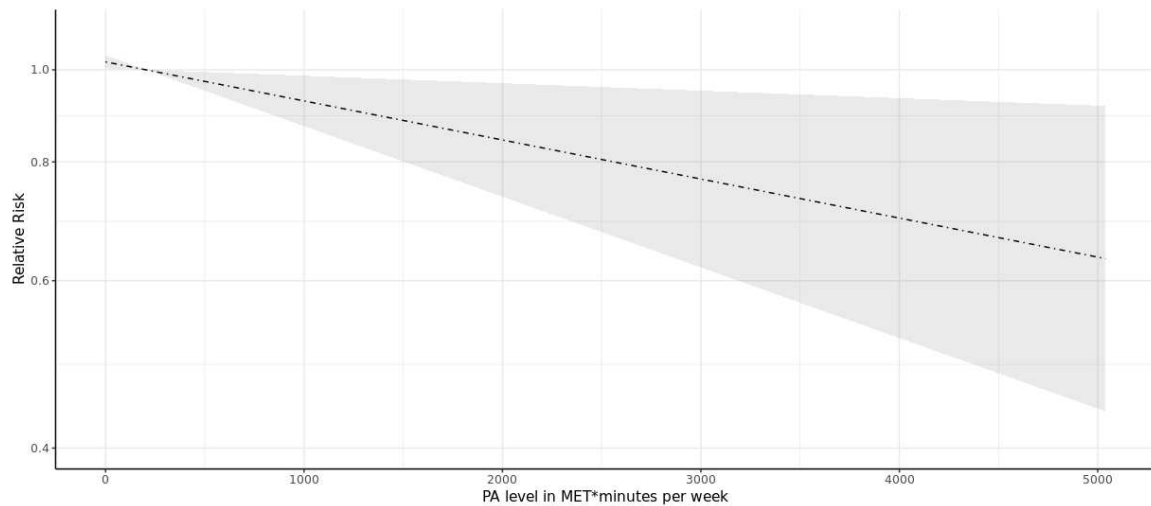
Q = 28.3221 (df = 18), p-value = 0.0573

I-square statistic = 36.4%

19 studies, 19 values, 1 fixed and 1 random-effects parameters

logLik	AIC	BIC
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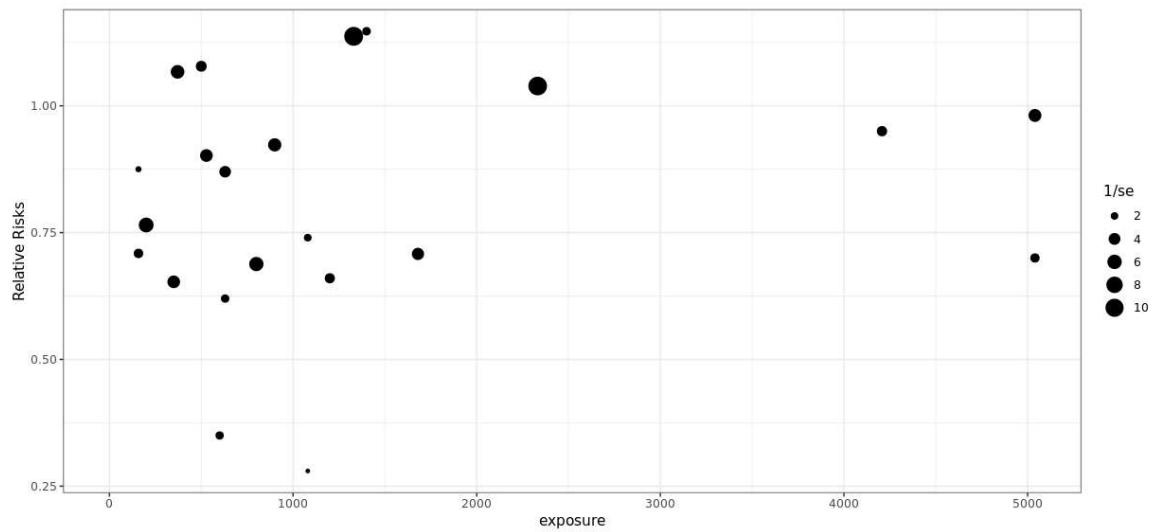
118.7244 -233.4489 -231.6681

Graphical prediction**Analytical predictions**

PA exposure	pred.lin	ci.lb.lin	ci.ub.lin
203.64	1.00	1.00	1.00
916.36	0.93	0.89	0.99
1934.55	0.85	0.74	0.97
2952.73	0.77	0.62	0.95
3970.91	0.70	0.52	0.93
4989.09	0.64	0.44	0.92

Models including studies with 3 or more PA exposure levels (AD)

Scatter plot of RRs vs original exposure variable



Linear Trend

```
Call: dosresmeta(formula = logrr ~ exposure, id = id, type = type,
  cases = cases, n = n, data = dataset(), se = se, covariance = input$pscorr)
```

Two-stage random-effects meta-analysis

Estimation method: REML

Covariance approximation: Greenland & Longnecker

Chi2 model: $X^2 = 2.1500$ (df = 1), p-value = 0.1426

Fixed-effects coefficients

	Estimate	Std. Error	z	Pr(> z)	95%ci.lb	95%ci.ub
(Intercept)	-0.0001	0.0001	-1.4663	0.1426	-0.0002	0.0000

Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Between-study random-effects (co)variance components

Std. Dev

0.0001

Univariate Cochran Q-test for residual heterogeneity:

Q = 10.8651 (df = 8), p-value = 0.2095

I-square statistic = 26.4%

9 studies, 9 values, 1 fixed and 1 random-effects parameters

logLik	AIC	BIC
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55.4683 -106.9365 -106.7776

Spline model

Call: dosresmeta(formula = logrr ~ rcs(exposure, knots), id = id, type = type, cases = cases, n = n, data = dataset(), se = se, covariance = input\$pscorr)

Two-stage random-effects meta-analysis

Estimation method: REML

Covariance approximation: Greenland & Longnecker

Chi2 model: $X^2 = 6.2649$ (df = 2), p-value = 0.0436

Fixed-effects coefficients

	Estimate	Std. Error	z	
rcs(exposure, knots)exposure.(Intercept)	-0.0004	0.0001	-2.4593	
rcs(exposure, knots)exposure'.(Intercept)	0.0003	0.0001	2.3245	
	Pr(> z)	95%ci.lb	95%ci.ub	
rcs(exposure, knots)exposure.(Intercept)	0.0139	-0.0007	-0.0001	*
rcs(exposure, knots)exposure'.(Intercept)	0.0201	0.0001	0.0006	*

Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Between-study random-effects (co)variance components

	Std. Dev	Corr
rcs(exposure, knots)exposure	0.0000	rcs(exposure, knots)exposure
rcs(exposure, knots)exposure'	0.0000	0.9723

Univariate Cochran Q-test for residual heterogeneity:

Q = 16.9974 (df = 16), p-value = 0.3858

I-square statistic = 5.9%

9 studies, 18 values, 2 fixed and 3 random-effects parameters

logLik	AIC	BIC
85.2275	-160.4549	-156.5920

Quadratic trend

Call: dosresmeta(formula = logrr ~ exposure + I(exposure^2), id = id, type = type, cases = cases, n = n, data = dataset(), se = se,

```

covariance = input$pscorr)

Two-stage random-effects meta-analysis
Estimation method: REML
Covariance approximation: Greenland & Longnecker

Chi2 model: X2 = 2.8700 (df = 2), p-value = 0.2381

Fixed-effects coefficients

```

	Estimate	Std. Error	z	Pr(> z)	95%ci.lb
exposure.(Intercept)	-0.0002	0.0001	-1.6085	0.1077	-0.0004
I(exposure^2).(Intercept)	0.0000	0.0000	1.3787	0.1680	-0.0000
	95%ci.ub				
exposure.(Intercept)	0.0000				
I(exposure^2).(Intercept)	0.0000				

```

---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Between-study random-effects (co)variance components

```

	Std. Dev	Corr
exposure	0.0002	exposure
I(exposure^2)	0.0000	-1

```

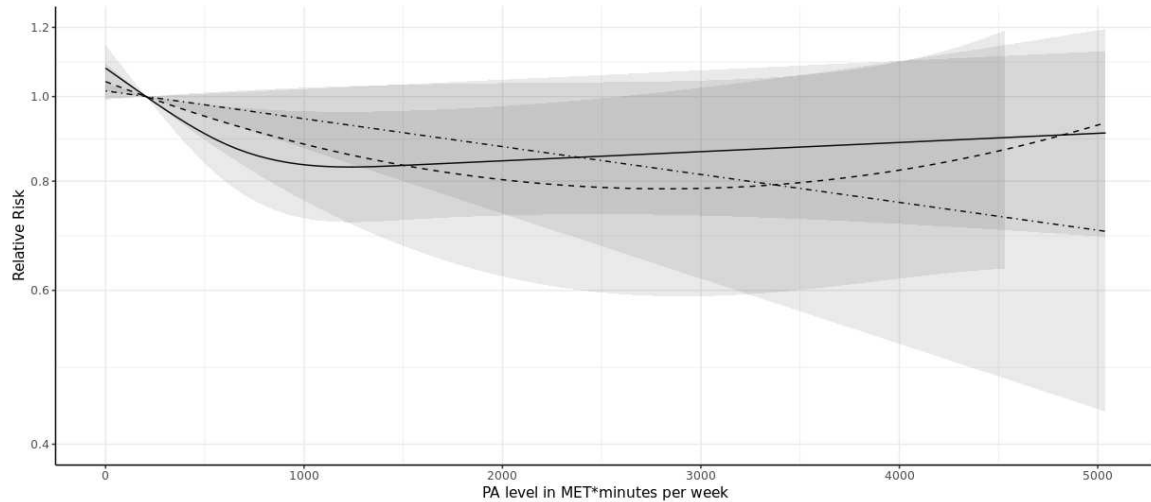
Univariate Cochran Q-test for residual heterogeneity:
Q = 19.6762 (df = 16), p-value = 0.2352
I-square statistic = 18.7%

9 studies, 18 values, 2 fixed and 3 random-effects parameters

```

logLik	AIC	BIC
158.5896	-307.1793	-303.3163

Graphical prediction



Linear Trend (dot-dash); Spline Model with knots at 20 and 80% of distribution (solid); Quadratic Trend (dashed)

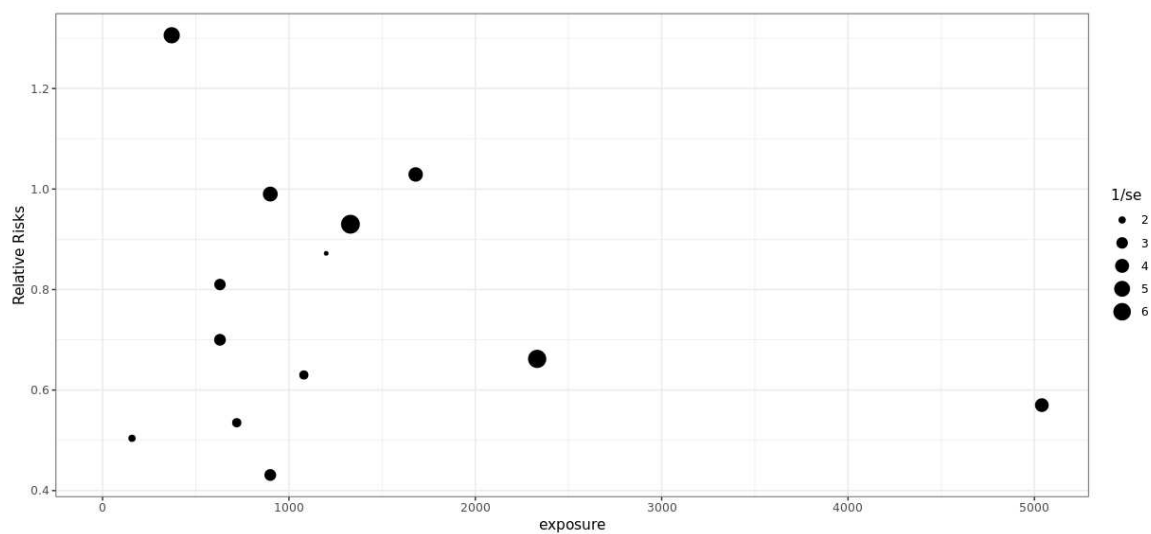
Analytical predictions

PA exposure	pred.lin	ci.lb.lin	ci.ub.lin	pred.spl	ci.lb.spl	ci.ub.spl	pred.quadr	ci.lb.quadr	ci.ub.quadr
203.64	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
916.36	0.95	0.88	1.02	0.84	0.73	0.96	0.89	0.78	1.02
1934.55	0.88	0.74	1.04	0.84	0.73	0.97	0.81	0.63	1.04
2952.73	0.82	0.62	1.07	0.86	0.73	1.02	0.78	0.59	1.04
3970.91	0.76	0.52	1.10	0.89	0.72	1.10	0.82	0.62	1.09
4989.09	0.70	0.44	1.13	0.91	0.69	1.19	0.93	0.64	1.34

Results - Vascular dementia (VD)

Linear model including all studies (VD)

Scatter plot of RRs vs original exposure variable



Linear Trend

```
Call: dosresmeta(formula = logrr ~ exposure, id = id, type = type,
  cases = cases, n = n, data = dataset(), se = se, covariance = input$pscorr)
```

Two-stage random-effects meta-analysis

Estimation method: REML

Covariance approximation: Greenland & Longnecker

Chi2 model: $X^2 = 14.3032$ (df = 1), p-value = 0.0002

Fixed-effects coefficients

	Estimate	Std. Error	z	Pr(> z)	95%ci.lb	95%ci.ub	
(Intercept)	-0.0002	0.0000	-3.7820	0.0002	-0.0003	-0.0001	***

Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Between-study random-effects (co)variance components

Std. Dev

0.0000

Univariate Cochran Q-test for residual heterogeneity:

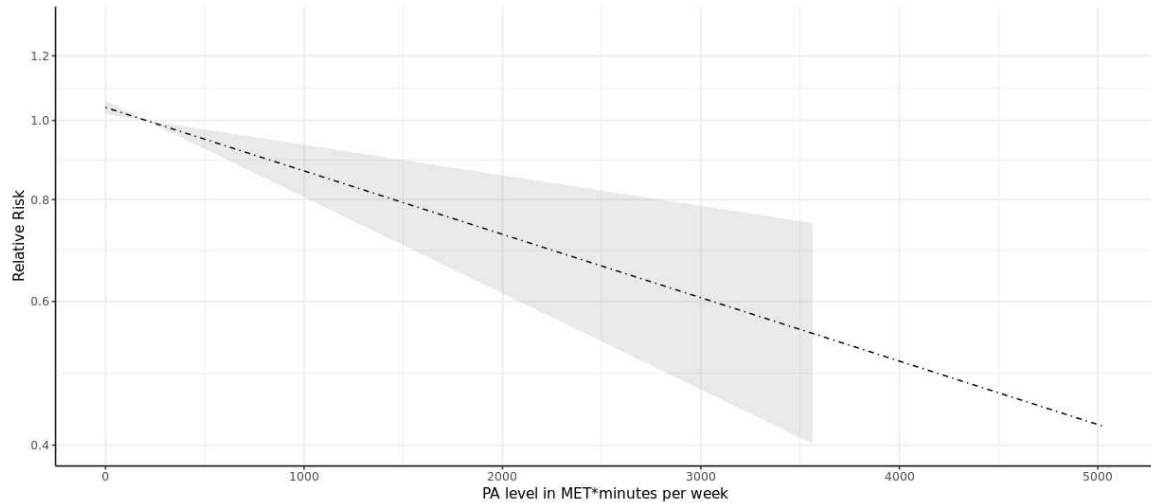
Q = 8.2459 (df = 7), p-value = 0.3114

I-square statistic = 15.1%

8 studies, 8 values, 1 fixed and 1 random-effects parameters

logLik	AIC	BIC
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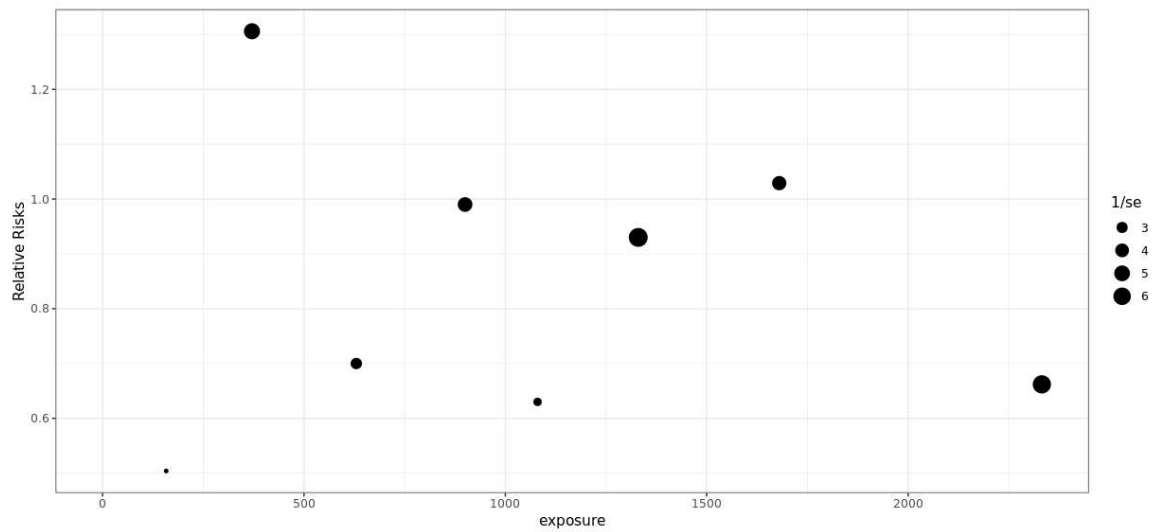
45.5563 -87.1126 -87.2208

Graphical prediction**Analytical predictions**

PA exposure	pred.lin	ci.lb.lin	ci.ub.lin
203.64	1.00	1.00	1.00
916.36	0.88	0.82	0.94
1934.55	0.73	0.62	0.86
2952.73	0.61	0.47	0.79
3970.91	0.51	0.36	0.72
4989.09	0.42	0.27	0.66

Models including studies with 3 or more PA exposure levels (VD)

Scatter plot of RRs vs original exposure variable



Linear Trend

```
Call: dosresmeta(formula = logrr ~ exposure, id = id, type = type,
  cases = cases, n = n, data = dataset(), se = se, covariance = input$pscorr)
```

Two-stage random-effects meta-analysis

Estimation method: REML

Covariance approximation: Greenland & Longnecker

Chi2 model: $X^2 = 7.8907$ (df = 1), p-value = 0.0050

Fixed-effects coefficients

	Estimate	Std. Error	z	Pr(> z)	95%ci.lb	95%ci.ub
(Intercept)	-0.0002	0.0001	-2.8090	0.0050	-0.0004	-0.0001 **

Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Between-study random-effects (co)variance components

Std. Dev

0.0000

Univariate Cochran Q-test for residual heterogeneity:

Q = 1.1021 (df = 2), p-value = 0.5764

I-square statistic = 0.0%

3 studies, 3 values, 1 fixed and 1 random-effects parameters

logLik	AIC	BIC
--------	-----	-----

14.2687 -24.5373 -27.1510

Spline model

Call: dosresmeta(formula = logrr ~ rcs(exposure, knots), id = id, type = type, cases = cases, n = n, data = dataset(), se = se, covariance = input\$pscorr)

Two-stage random-effects meta-analysis

Estimation method: REML

Covariance approximation: Greenland & Longnecker

Chi2 model: X2 = 8.1864 (df = 2), p-value = 0.0167

Fixed-effects coefficients

	Estimate	Std. Error	z
rcs(exposure, knots)exposure.(Intercept)	-0.0001	0.0003	-0.1959
rcs(exposure, knots)exposure'.(Intercept)	-0.0001	0.0003	-0.5438
	Pr(> z)	95%ci.lb	95%ci.ub
rcs(exposure, knots)exposure.(Intercept)	0.8447	-0.0006	0.0005
rcs(exposure, knots)exposure'.(Intercept)	0.5866	-0.0007	0.0004

Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Between-study random-effects (co)variance components

	Std. Dev	Corr
rcs(exposure, knots)exposure	0.0000	rcs(exposure, knots)exposure
rcs(exposure, knots)exposure'	0.0000	-0.9995

Univariate Cochran Q-test for residual heterogeneity:

Q = 1.5369 (df = 4), p-value = 0.8201

I-square statistic = 0.0%

3 studies, 6 values, 2 fixed and 3 random-effects parameters

logLik	AIC	BIC
24.6521	-39.3042	-42.3727

Quadratic trend

Call: dosresmeta(formula = logrr ~ exposure + I(exposure^2), id = id, type = type, cases = cases, n = n, data = dataset(), se = se,

```

covariance = input$pscorr)

Two-stage random-effects meta-analysis
Estimation method: REML
Covariance approximation: Greenland & Longnecker

Chi2 model: X2 = 8.5347 (df = 2), p-value = 0.0140

Fixed-effects coefficients

```

	Estimate	Std. Error	z	Pr(> z)	95%ci.lb
exposure.(Intercept)	-0.0000	0.0003	-0.0541	0.9568	-0.0005
I(exposure^2).(Intercept)	-0.0000	0.0000	-0.8025	0.4223	-0.0000
	95%ci.ub				
exposure.(Intercept)	0.0005				
I(exposure^2).(Intercept)	0.0000				

```

---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Between-study random-effects (co)variance components

```

	Std. Dev	Corr
exposure	0.0000	exposure
I(exposure^2)	0.0000	0.9446

```

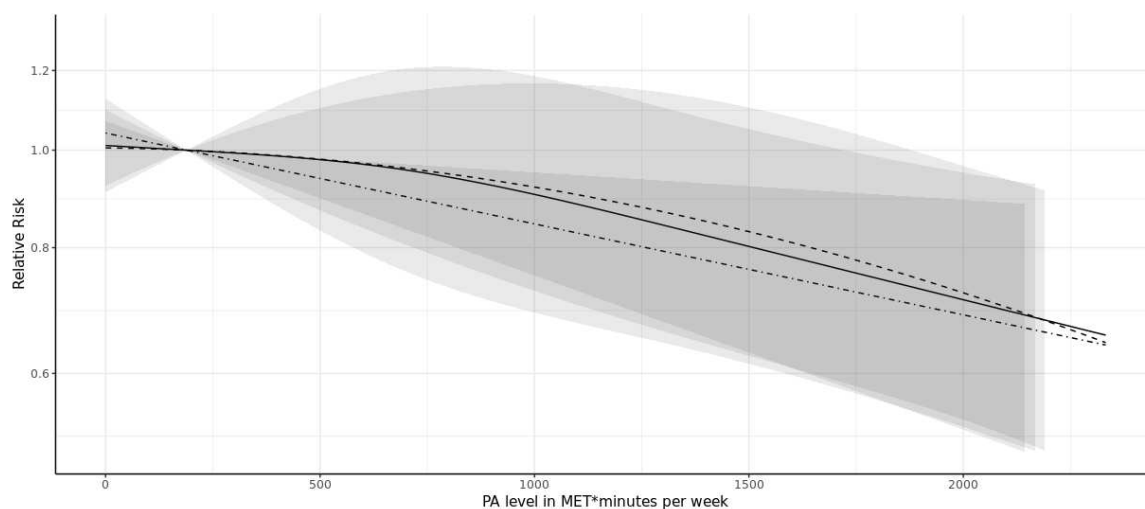
Univariate Cochran Q-test for residual heterogeneity:
Q = 1.2812 (df = 4), p-value = 0.8646
I-square statistic = 0.0%

3 studies, 6 values, 2 fixed and 3 random-effects parameters

```

logLik	AIC	BIC
40.3790	-70.7581	-73.8266

Graphical prediction



Linear Trend (dot-dash); Spline Model with knots at 20 and 80% of distribution (solid); Quadratic Trend (dashed)

Analytical predictions

PA exposure	pred.lin	ci.lb.lin	ci.ub.lin	pred.spl	ci.lb.spl	ci.ub.spl	pred.quadr	ci.lb.quadr	ci.ub.quadr
188.48	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
424.00	0.95	0.92	0.99	0.98	0.87	1.12	0.99	0.90	1.08
895.11	0.86	0.78	0.96	0.92	0.71	1.20	0.93	0.75	1.16
1366.22	0.78	0.66	0.93	0.83	0.63	1.08	0.86	0.65	1.13
1837.33	0.71	0.56	0.90	0.74	0.56	0.98	0.76	0.57	1.01
2308.44	0.64	0.47	0.88	0.66	0.48	0.91	0.65	0.48	0.88

References

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