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Marginal proportional hazards models for multivariate interval-censored data

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Outline

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Introduction

Multivariate Failure Time Data

- Multiple events: each subject can potentially experience several events
- Cluster: natural/artificial clustering of study subjects

Interval Censoring: Failure occurs within a time interval

Medical Research: Periodic monitoring of asymptomatic diseases

- diabetes and hypertension in family members
- asymptomatic SARS-Cov-2 infection

Theoretical/Computational Issues

- no exact failure time
- unknown dependence structures

Existing methods

Random-effects models for multivariate interval-censored data

- Chen et al. (2009): current-status data
- Chen et al. (2014): a common set of examination times for all subjects
- Wen & Chen (2013): asymptotic theory for bivariate interval-censored data
- Chang et al. (2007): asymptotic theory for current-status family data
- Zeng et al. (2017): transformation models for general multivariate interval-censored data

Marginal models for multivariate interval-censored data

- assume examinations occur at a common set of time points
- parameterize the event time distribution
- Goggins & Finkelstein, 2000; Kim & Xue, 2002; Chen et al., 2007; Tong et al., 2008; Chen et al., 2013; Shen, 2015; Zhang & Sun, 2010; Kor et al., 2013

Outline

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Notation

- n = number of clusters
- n_i = number of subjects in the ith cluster
- K = number of types of failures
- $X_{ijk}(\cdot)$ = (potentially time-dependent) covariates
- T_{ijk} = kth failure time for the jth subject of the ith cluster
- $U_{ijk1} < \cdots < U_{ijk,M_{ijk}}$ = random sequence of examination times on T_{ijk}
- $(L_{ijk}, R_{ijk}]$ = the shortest time interval that brackets T_{ijk}

Data, models and pseudo-likelihood

Data: $(L_{ijk}, R_{ijk}, X_{ijk})$ $(i = 1, \ldots, n; j = 1, \ldots, n_i; k = 1, \ldots, K)$

Marginal Proportional Hazards Models

$$\lambda_{ijk}(t) = \lambda_k(t) \exp\left\{\beta_k^{\mathrm{T}} X_{ijk}(t)\right\}$$

- β_k = regression parameters
- $\lambda_k(t)$ = arbitrary baseline hazard function
- $\Lambda_k(t) = \int_0^t \lambda_k(s)\mathrm{d}s$

Pseudo-Likelihood

$$\prod_{i=1}^{n}\prod_{j=1}^{n_i}\prod_{k=1}^{K}\left[\exp\left\{-\int_0^{L_{ijk}} e^{\beta_k^{\mathrm{T}} X_{ijk}(t)}\mathrm{d}\Lambda_k(t)\right\} - \exp\left\{-\int_0^{R_{ijk}} e^{\beta_k^{\mathrm{T}} X_{ijk}(t)}\mathrm{d}\Lambda_k(t)\right\}\right]$$

Estimation procedure

Nonparametric Maximum Pseudo-Likelihood Estimation

- $0 < t_{k0} < t_{k1} < \cdots < t_{km_k} < \infty = \{L_{ijk} > 0, R_{ijk} < \infty; i = 1, \ldots, n; j = 1, \ldots, n_i\}$
- λ_{kq} = jump size of $\Lambda_k(\cdot)$ at t_{kq}
- $X_{ijkq} = X_{ijk}(t_{kq})$
- For each k, we maximize

$$\prod_{i=1}^{n}\prod_{j=1}^{n_i}\left\{\exp\left(-\sum_{t_{kq}\leqslant L_{ijk}}\lambda_{kq}e^{\beta_k^{\mathrm{T}}X_{ijkq}}\right)-I(R_{ijk}<\infty)\exp\left(-\sum_{t_{kq}\leqslant R_{ijk}}\lambda_{kq}e^{\beta_k^{\mathrm{T}}X_{ijkq}}\right)\right\}$$

Estimation procedure

Implementation

- Direct maximization
  - non-concave likelihood
  - no analytic expression for λ_{kq}
  - many λ_{kq} are zero
- EM-type algorithm
  - latent Poisson variables with same observed-data likelihood
  - analytic expression for λ_{kq}
  - partial-likelihood like estimating equation for β_k
  - observed-data pseudo-likelihood increases at each iteration

EM-type algorithm

Latent variables: $W_{ijkq} \overset{\text{ind}}{\sim} \text{Poisson}\left(\lambda_{kq} e^{\beta_k^{\mathrm{T}} X_{ijkq}}\right)$

$(i = 1, \ldots, n; j = 1, \ldots, n_i; k = 1, \ldots, K; q = 1, \ldots, m_k)$

Observed data: $(L_{ijk}, R_{ijk}, X_{ijk}, A_{ijk} = 0, B_{ijk} > 0)$

- $A_{ijk} = \sum_{t_{kq} \leqslant L_{ijk}} W_{ijkq}$
- $B_{ijk} = I\left(R_{ijk} < \infty\right) \sum_{L_{ijk} < t_{kq} \leqslant R_{ijk}} W_{ijkq}$

Observed-data likelihood

$$\prod_{i=1}^{n} \prod_{j=1}^{n_i} \left\{ \prod_{t_{kq} \leqslant L_{ijk}} \Pr\left(W_{ijkq} = 0\right) \right\} \left\{ 1 - \Pr\left(\sum_{L_{ijk} < t_{kq} \leqslant R_{ijk}} W_{ijkq} = 0 \right) \right\}^{I(R_{ijk} < \infty)}$$

Complete-data log-likelihood

$$\sum_{i=1}^{n} \sum_{j=1}^{n_i} \sum_{q=1}^{m_k} I(R_{ijk}^{*} \geqslant t_{kq}) \left\{ W_{ijkq} \log(\lambda_{kq} e^{\beta_k^{\mathrm{T}} X_{ijkq}}) - \lambda_{kq} e^{\beta_k^{\mathrm{T}} X_{ijkq}} - \log W_{ijkq}! \right\},$$

- $R_{ijk}^{*} = I(R_{ijk} < \infty) R_{ijk} + I(R_{ijk} = \infty) L_{ijk}$

EM-type algorithm

E-step

$$\widehat{E}(W_{ijkq}) = I(L_{ijk} < t_{kq} \leqslant R_{ijk} < \infty) \frac{\lambda_{kq} \exp(\beta_k^{\mathrm{T}} X_{ijkq})}{1 - \exp\{-\sum_{L_{ijk} < t_{kq'} \leqslant R_{ijk}} \lambda_{kq'} \exp(\beta_k^{\mathrm{T}} X_{ijkq'})\}}.$$

M-step

$$\sum_{i=1}^{n} \sum_{j=1}^{n_i} \sum_{q=1}^{m_k} I(R^*_{ijk} \geqslant t_{kq}) \widehat{E}(W_{ijkq}) \times \left\{ X_{ijkq} - \frac{\sum_{i'=1}^{n} \sum_{j'=1}^{n_{i'}} I(R^*_{i'j'k} \geqslant t_{kq}) \exp(\beta_k^{\mathrm{T}} X_{i'j'kq}) X_{i'j'kq}}{\sum_{i'=1}^{n} \sum_{j'=1}^{n_{i'}} I(R^*_{i'j'k} \geqslant t_{kq}) \exp(\beta_k^{\mathrm{T}} X_{i'j'kq})} \right\} = 0.$$

We then update

$$\lambda_{kq} = \frac{\sum_{i=1}^{n} \sum_{j=1}^{n_i} I(R^*_{ijk} \geqslant t_{kq}) \widehat{E}(W_{ijkq})}{\sum_{i=1}^{n} \sum_{j=1}^{n_i} I(R^*_{ijk} \geqslant t_{kq}) \exp(\beta_k^{\mathrm{T}} X_{ijkq})}$$

Asymptotic properties

Let $\widehat{\beta} = \left(\widehat{\beta}_1^{\mathrm{T}}, \ldots, \widehat{\beta}_K^{\mathrm{T}}\right)^{\mathrm{T}}$ and $\widehat{\Lambda} = \left(\widehat{\Lambda}_1, \ldots, \widehat{\Lambda}_K\right)$.

Consistency

Theorem 1

Under some regularity conditions, $\|\widehat{\beta} - \beta_0\| + \sum_{k=1}^{K} \sup_{t \in [0, \tau_k]} |\widehat{\Lambda}_k(t) - \Lambda_{0k}(t)| \to 0$ *almost surely, where* $\|\cdot\|$ *is the Euclidean norm.*

Asymptotic distribution

Theorem 2

Under some regularity conditions, $n^{1/2}(\widehat{\beta} - \beta_0)$ *converges in distribution to a zero-mean multivariate normal random vector with covariance matrix* Ω.

Sandwich variance estimator

Profile pseudo-log-likelihood for β_k

$$\mathrm{pl}_k(\beta_k) = \sum_{i=1}^{n}\sum_{j=1}^{n_i} \log\left\{ \exp\left(- \sum_{t_{kq}\leqslant L_{ijk}} \widetilde{\lambda}_{kq} e^{\beta_k^{\mathrm{T}} X_{ijkq}} \right) - I\left(R_{ijk} < \infty\right) \exp\left(- \sum_{t_{kq}\leqslant R_{ijk}} \widetilde{\lambda}_{kq} e^{\beta_k^{\mathrm{T}} X_{ijkq}} \right) \right\}$$

- $\widetilde{\lambda}_{kq}\,(q = 1, \ldots, m_k)$ are obtained from EM with fixed β_k

Covariance matrix estimator between $\widehat{\beta}_k$ and $\widehat{\beta}_l$

$$\widehat{V}_{kl} = \left\{ D_{h_n}^2 \mathrm{pl}_k(\widehat{\beta}_k) \right\}^{-1} \sum_{i=1}^{n} D_{h_n}\mathrm{pl}_{ki}(\widehat{\beta}_k) D_{h_n}\mathrm{pl}_{li}(\widehat{\beta}_l)^{\mathrm{T}} \left\{ D_{h_n}^2 \mathrm{pl}_l(\widehat{\beta}_l) \right\}^{-1}$$

- $\mathrm{pl}_{ki}\left(\beta_k\right) =$ contribution of the i th cluster to $pl_k\left(\beta_k\right)$

Sandwich variance estimator

Theorem 3

Under some regularity conditions, $\{n(\widehat{V}_{kl}); 1 \leqslant k, l \leqslant K\}$ is a consistent estimator for the limiting covariance matrix Ω.

Statistical Inference

$$L\widehat{\beta} \sim N\left(L\beta, LVL'\right)$$

$$V = \begin{bmatrix} V_{11} & \cdots & V_{1K} \\ \vdots & \vdots & \vdots \\ V_{K1} & \cdots & V_{KK} \end{bmatrix}$$

- linear combinations (e.g., a subset of parameters, difference of two parameters)

Outline

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Simulation studies

Clustered data

- $K = 1$
- n_i varies from 1 to 5 with probabilities 0.1, 0.5, 0.2, 0.1 and 0.1
- Treatment assignment: cluster-level $X_1 \sim \mathrm{Ber}(0.5)$
- Correlated continuous covariate: subject-level $X_2 = X_1^* + X_2^*$
  - cluster-level $X_1^* \sim \mathrm{Un}(0, 1)$
  - subject-level $X_2^* = \max\{0, N(0, 0.04)\}$
- $\beta_1 = 0.5$, $\beta_2 = -0.5$
- Generate $(Z_1, \ldots, Z_{n_i}) \sim N_{n_i}(0, \Sigma)$ and $T_j^* = -\mu \log\{1 - \Phi(Z_j)\}$
  - Σ is an exchangeable correlation matrix with $\rho = 0.2$, 0.5 or 0.75
  - $\mu = 2 \exp\{-(\beta_1 X_1 + \beta_2 X_2)\}$
- Event times: $T_j = T_j^{*2}$
- Cumulative hazard function: $0.5 t^{1/2} \exp(\beta_1 X_1 + \beta_2 X_2)$

Simulation studies

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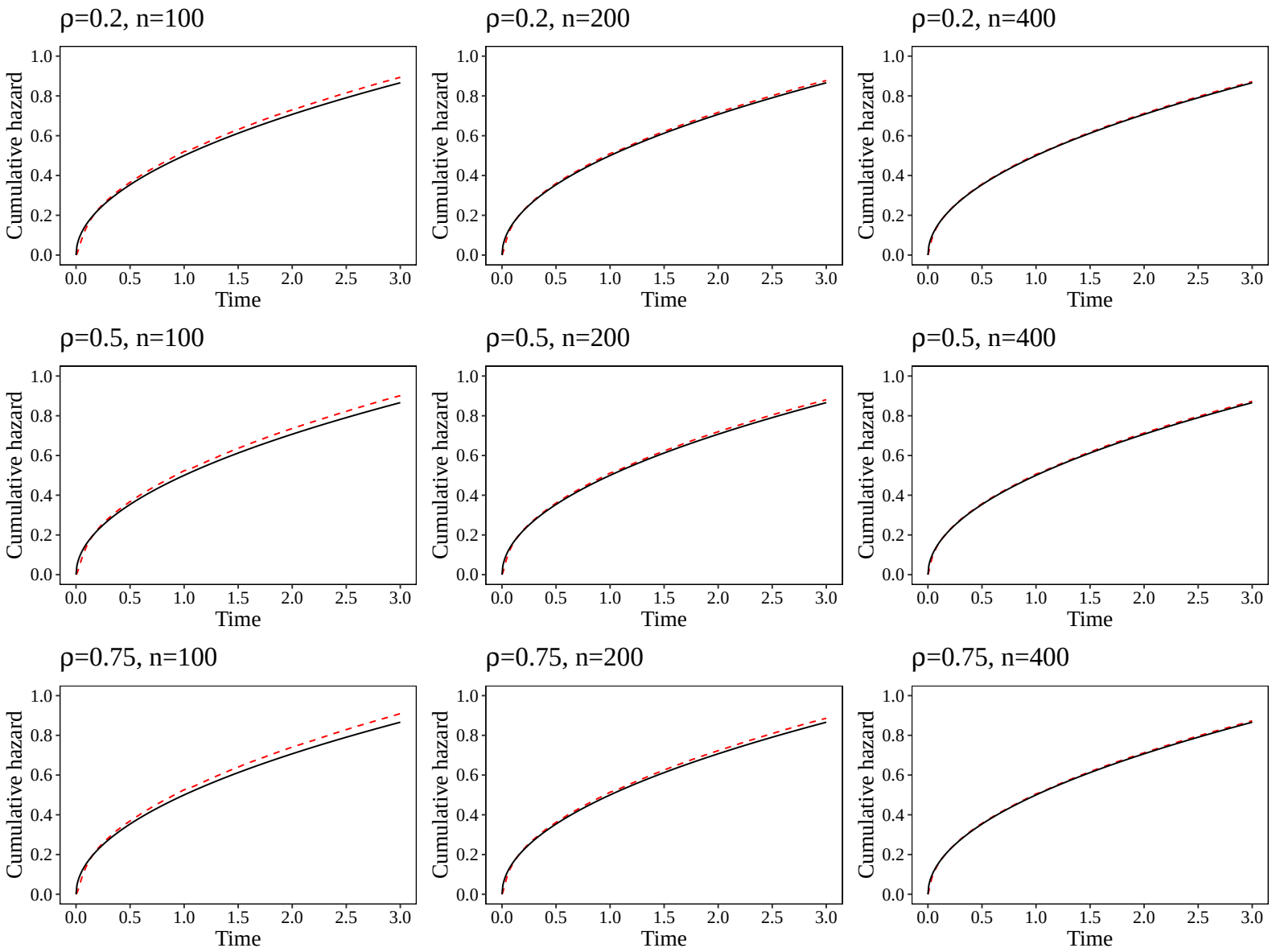
Table 1. *Parameter estimation results for simulation studies with clustered data*

			Marginal model						Random-effects model			
ρ	No. of clusters	Parameter	Bias	SE	SEE	CP	SEEn	CPn	Bias	SE	SEE	CP
0.2	$n = 100$	$\beta_1 = 0.5$	0.005	0.202	0.211	95.5	0.182	92.0	0.060	0.222	0.220	94.2
		$\beta_2 = -0.5$	−0.012	0.314	0.314	94.8	0.279	91.9	−0.064	0.355	0.344	94.2
	$n = 200$	$\beta_1 = 0.5$	0.005	0.142	0.145	95.4	0.125	91.6	0.060	0.157	0.154	93.1
		$\beta_2 = -0.5$	−0.006	0.219	0.216	94.6	0.194	91.7	−0.069	0.244	0.241	94.2
	$n = 400$	$\beta_1 = 0.5$	0.003	0.097	0.100	95.7	0.087	92.3	0.059	0.110	0.109	91.7
		$\beta_2 = -0.5$	−0.004	0.154	0.152	94.5	0.136	91.5	−0.061	0.171	0.170	93.4
0.5	$n = 100$	$\beta_1 = 0.5$	0.007	0.238	0.247	95.7	0.182	86.8	0.224	0.335	0.326	89.4
		$\beta_2 = -0.5$	−0.013	0.369	0.359	94.1	0.279	86.5	−0.229	0.493	0.483	92.6
	$n = 200$	$\beta_1 = 0.5$	0.004	0.165	0.169	95.6	0.125	86.5	0.215	0.233	0.227	84.7
		$\beta_2 = -0.5$	−0.005	0.253	0.249	94.5	0.194	86.7	−0.210	0.340	0.336	90.7
	$n = 400$	$\beta_1 = 0.5$	0.002	0.114	0.118	95.7	0.087	86.5	0.209	0.162	0.160	74.6
		$\beta_2 = -0.5$	−0.002	0.178	0.174	94.6	0.136	87.0	−0.209	0.238	0.236	85.7
0.75	$n = 100$	$\beta_1 = 0.5$	0.013	0.266	0.278	95.9	0.182	82.2	0.515	0.521	0.493	82.2
		$\beta_2 = -0.5$	−0.013	0.410	0.399	93.9	0.279	82.2	−0.519	0.699	0.677	88.4
	$n = 200$	$\beta_1 = 0.5$	0.006	0.184	0.191	95.6	0.125	82.0	0.527	0.359	0.346	67.0
		$\beta_2 = -0.5$	−0.007	0.285	0.277	94.2	0.194	81.7	−0.524	0.491	0.473	80.0
	$n = 400$	$\beta_1 = 0.5$	0.004	0.130	0.132	95.4	0.087	81.4	0.516	0.254	0.239	42.8
		$\beta_2 = -0.5$	−0.001	0.197	0.194	94.4	0.136	82.6	−0.506	0.338	0.331	66.4

SE, standard error of the parameter estimator; SEE, mean of the proposed standard error estimator; SEEn, mean of the naive standard error estimator; CP, coverage percentage of the 95% confidence interval based on the sandwich variance estimator; CPn, coverage percentage of the 95% confidence interval based on the naive variance estimator.

Simulation studies



Simulation studies

Multiple-event data

- $K = 2$
- $n_i = 1$
- Subject-level $X_1 \sim \mathrm{Ber}(0.5)$ and $X_2 = \mathrm{Un}(0, 1)$
- $(\beta_{11}, \beta_{12}) = (0.5, -0.5)$ and $(\beta_{21}, \beta_{22}) = (0.5, 0.5)$
- Generate $T_j^* = -\mu_j \log\{1 - \Phi(Z_j)\}$ $(j = 1, 2)$
  - (Z_1, Z_2): standard normal with correlation $\rho = 0.2$, 0.5 or 0.75
  - $\mu_1 = 2 \exp\{-(\beta_{11}X_1 + \beta_{12}X_2)\}$
  - $\mu_2 = 5 \exp\{-(\beta_{21}X_1 + \beta_{22}X_2)\}$
- Event times: $(T_1, T_2) = (T_1^{*2}, T_2^*)$

Simulation studies

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Table 2. *Parameter estimation results for simulation studies with multiple-event data*

		First event				Second event				Optimal combination			
ρ	No. of subjects	Bias	SE	SEE	CP	Bias	SE	SEE	CP	Bias	SE	SEE	CP
0.2	$n = 100$	0.019	0.287	0.297	95.9	0.018	0.281	0.289	95.8	0.007	0.213	0.223	96.0
	$n = 200$	0.009	0.196	0.202	95.8	0.010	0.191	0.196	95.7	0.005	0.147	0.151	95.5
	$n = 400$	0.005	0.136	0.139	95.5	0.006	0.134	0.135	95.2	0.004	0.103	0.104	95.1
0.5	$n = 100$	0.020	0.285	0.297	96.2	0.026	0.280	0.289	96.0	0.011	0.232	0.248	96.3
	$n = 200$	0.010	0.195	0.202	95.9	0.014	0.191	0.196	95.8	0.008	0.160	0.167	96.1
	$n = 400$	0.007	0.138	0.139	95.4	0.007	0.133	0.135	95.7	0.005	0.112	0.115	95.7
0.75	$n = 100$	0.020	0.282	0.297	96.2	0.021	0.276	0.289	96.0	0.004	0.260	0.268	96.5
	$n = 200$	0.009	0.195	0.202	96.0	0.009	0.188	0.195	95.8	0.003	0.170	0.180	96.4
	$n = 400$	0.006	0.136	0.139	95.7	0.010	0.134	0.135	95.2	0.006	0.120	0.124	95.8

SE, standard error of the parameter estimator; SEE, mean of the proposed standard error estimator; CP, coverage percentage of the 95% confidence interval based on the proposed variance estimator.

Outline

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ARIC study

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Atherosclerosis Risk in Communities Study (ARIC): cohort of 14,751 white and black individuals from 4 U.S. communities

Examinations: 1987–1989 → (3-year intervals) → 2011–2013

Diabetes

- fasting glucose $\geqslant 126 \mathrm{mg/dL}$
- non-fasting glucose $\geqslant 200 \mathrm{mg/dL}$
- self-reported physician diagnosis of diabetes
- use of diabetic medication

Hypertension:

- systolic blood pressure $\geqslant 140$
- diastolic blood pressure $\geqslant 90$
- use of anti-hypertensive medication

Analysis set: 8,735 individuals without prior diabetes or hypertension

ARIC study

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Table 3. *Regression analysis of the Atherosclerosis Risk in Communities Study*

	Diabetes			Hypertension			Overall test		Difference		
Risk factor	Est	SE	p-value	Est	SE	p-value	Test	p-value	Est	SE	95% CI
Jackson	−0.145	0.149	0.332	−0.239	0.077	0.002	10.14	0.006	0.094	0.162	(−0.234, 0.413)
Minneapolis suburbs	−0.389	0.076	$< 10^{-4}$	−0.100	0.046	0.031	29.17	$< 10^{-4}$	−0.289	0.085	(−0.455, −0.122)
Washington County	0.115	0.073	0.114	0.078	0.048	0.103	4.68	0.096	0.037	0.083	(−0.125, 0.199)
Age	−0.014	0.005	0.007	0.013	0.003	$< 10^{-4}$	26.17	$< 10^{-4}$	−0.027	0.006	(−0.038, −0.016)
Male	−0.062	0.055	0.265	−0.238	0.034	$< 10^{-4}$	49.34	$< 10^{-4}$	0.176	0.062	(0.056, 0.297)
Caucasian	−0.451	0.160	0.005	−0.480	0.081	$< 10^{-4}$	40.29	$< 10^{-4}$	0.029	0.172	(−0.307, 0.366)
Body mass index (kg/m^2)	0.075	0.005	$< 10^{-4}$	0.017	0.004	$< 10^{-4}$	236.83	$< 10^{-4}$	0.059	0.006	(0.047, 0.070)
Derived glucose value (mg/dl)	0.096	0.003	$< 10^{-4}$	0.001	0.002	0.595	961.78	$< 10^{-4}$	0.095	0.004	(0.088, 0.102)
Systolic blood pressure (mmHg)	0.005	0.003	0.096	0.058	0.002	$< 10^{-4}$	914.31	$< 10^{-4}$	−0.053	0.003	(−0.060, −0.046)
Diastolic blood pressure (mmHg)	0.005	0.004	0.310	0.011	0.003	$< 10^{-4}$	17.48	0.0002	−0.007	0.005	(−0.016, 0.003)

Est, estimate; SE, standard error; CI, confidence interval.

Outline

Future work

- Model checking
- A more flexible working dependence structure
- Intermittent missing values or measurement error of covariates

Thank you!