Web-based Supporting Materials for Testing Departure from Additivity in Tukey's Model using Shrinkage: Application to a Longitudinal Setting

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1 Variance Estimation for the Shrinkage Estimator

The asymptotic variance-covariance matrix of $\hat{\phi}$, denoted by $\boldsymbol{\Sigma}_{\hat{\boldsymbol{\phi}}}$, is given by

$$\begin{bmatrix} \boldsymbol{\mathcal{I}}^{-1}\text{var}\big(\sum_k \dot{\ell}_k\big)(\boldsymbol{\mathcal{I}}^{-1})^\top & \boldsymbol{\mathcal{I}}^{-1}\text{cov}\big(\sum_k \dot{\ell}_k, \sum_k \dot{\ell}_{0k}\big)(\boldsymbol{\mathcal{I}}_0^{-1})^\top \\ \boldsymbol{\mathcal{I}}_0^{-1}\text{cov}\big(\sum_k \dot{\ell}_{0k}, \sum_k \dot{\ell}_k\big)(\boldsymbol{\mathcal{I}}^{-1})^\top & \boldsymbol{\mathcal{I}}_0^{-1}\text{var}\big(\sum_k \dot{\ell}_{0k}\big)(\boldsymbol{\mathcal{I}}_0^{-1})^\top \end{bmatrix},$$

where $\dot{\ell}_k$ and $\dot{\ell}_{0k}$ are the individual score functions for the saturated interaction model and Tukey's model, respectively. When $N \to \infty$, var$(\sum_k \dot{\ell}_k) \to \boldsymbol{\mathcal{I}}$ and var$(\sum_k \dot{\ell}_{0k}) \to \boldsymbol{\mathcal{I}}_0$. To estimate $\boldsymbol{\Sigma}_{\hat{\boldsymbol{\phi}}}$, we replace $\boldsymbol{\mathcal{I}}$ and $\boldsymbol{\mathcal{I}}_0$ by observed information matrices evaluated at $\hat{\boldsymbol{\phi}}$. The covariance of $\boldsymbol{\Sigma}_{\hat{\boldsymbol{\phi}}}$ can be estimated as

$$\hat{\text{cov}}\big(\sum_k \dot{\ell}_k, \sum_k \dot{\ell}_{0k}\big) = \frac{1}{N^2}\Big\{\sum_k \dot{\ell}_k(\hat{\boldsymbol{\eta}}_{sat})[\dot{\ell}_{0k}(\hat{\boldsymbol{\eta}}_{tuk})]^\top - \frac{1}{N}\sum_k \dot{\ell}_k(\hat{\boldsymbol{\eta}}_{sat})\sum_k \dot{\ell}_{0k}(\hat{\boldsymbol{\eta}}_{tuk})\Big\}$$

and its transpose. Recall that

$$\boldsymbol{h}(\hat{\boldsymbol{\phi}}) = \hat{\boldsymbol{\xi}} = \begin{bmatrix} \hat{\boldsymbol{\tau}}_{sat} \\ \hat{\boldsymbol{\tau}}_{tuk} \end{bmatrix}.$$

The gradient matrix $\bigtriangledown \boldsymbol{h}(\hat{\boldsymbol{\phi}})$ is given by

$$\bigtriangledown \boldsymbol{h}(\hat{\boldsymbol{\phi}}) = \begin{bmatrix} \boldsymbol{I}_{(I-1)(J-1)} & & & \mathbf{0} & & & \\ & \hat{\lambda}\hat{\beta}_1^E & 0 & \dots & \hat{\lambda}\hat{\beta}_2^E & 0 & \dots \\ & 0 & \hat{\lambda}\hat{\beta}_1^E & \dots & \hat{\lambda}\hat{\beta}_2^E & 0 & \dots \\ \mathbf{0} & \vdots & \vdots & \vdots & \vdots & \vdots & \vdots \\ & \hat{\lambda}\hat{\beta}_1^G & \hat{\lambda}\hat{\beta}_2^G & \dots & 0 & 0 & \dots \\ & 0 & 0 & \dots & \hat{\lambda}\hat{\beta}_1^G & \hat{\lambda}\hat{\beta}_2^G & \dots \\ & \vdots & \vdots & \vdots & \vdots & \vdots & \vdots \\ & \hat{\beta}_1^G\hat{\beta}_1^E & \hat{\beta}_2^G\hat{\beta}_1^E & \dots & \dots & \dots & \dots \end{bmatrix}.$$

Next, we want to derive $\bigtriangledown \boldsymbol{g}(\hat{\boldsymbol{\xi}})$. Note that the shrinkage estimator can be expressed as

$$\begin{aligned}
\hat{\boldsymbol{\tau}}_{shk} = g(\hat{\boldsymbol{\xi}}) = g(\hat{\boldsymbol{\tau}}_{tuk}, \hat{\boldsymbol{\tau}}_{sat}) &= \hat{\boldsymbol{\tau}}_{sat} + \boldsymbol{B}(\hat{\boldsymbol{\tau}}_{tuk} - \hat{\boldsymbol{\tau}}_{sat}) \\
&= \hat{\boldsymbol{\tau}}_{sat} + \hat{\boldsymbol{V}}_\tau(\hat{\boldsymbol{V}}_\tau + \hat{\boldsymbol{\delta}}\hat{\boldsymbol{\delta}}^\top)^{-1}\hat{\boldsymbol{\delta}} \\
&= \hat{\boldsymbol{\tau}}_{sat} + \hat{\boldsymbol{V}}_\tau\left(\hat{\boldsymbol{V}}_\tau^{-1} - \frac{\hat{\boldsymbol{V}}_\tau^{-1}\hat{\boldsymbol{\delta}}\hat{\boldsymbol{\delta}}^\top\hat{\boldsymbol{V}}_\tau^{-1}}{1+\hat{\boldsymbol{\delta}}^\top\hat{\boldsymbol{V}}_\tau^{-1}\hat{\boldsymbol{\delta}}}\right)\hat{\boldsymbol{\delta}} \\
&= \hat{\boldsymbol{\tau}}_{sat} + \hat{\boldsymbol{\delta}} - \frac{\hat{\boldsymbol{\delta}}\hat{\boldsymbol{\delta}}^\top\hat{\boldsymbol{V}}_\tau^{-1}\hat{\boldsymbol{\delta}}}{1+\hat{\boldsymbol{\delta}}^\top\hat{\boldsymbol{V}}_\tau^{-1}\hat{\boldsymbol{\delta}}} \\
&= \hat{\boldsymbol{\tau}}_{tuk} - \frac{\hat{\boldsymbol{\delta}}\hat{\boldsymbol{\delta}}^\top\hat{\boldsymbol{V}}_\tau^{-1}\hat{\boldsymbol{\delta}}}{1+\hat{\boldsymbol{\delta}}^\top\hat{\boldsymbol{V}}_\tau^{-1}\hat{\boldsymbol{\delta}}}, \quad \hat{\boldsymbol{\delta}} = \hat{\boldsymbol{\tau}}_{tuk} - \hat{\boldsymbol{\tau}}_{sat}.
\end{aligned}$$

Then the $(I-1)(J-1) \times 2(I-1)(J-1)$ matrix $\bigtriangledown \boldsymbol{g}(\hat{\boldsymbol{\xi}}) = \frac{\partial \boldsymbol{g}}{\partial \boldsymbol{\xi}}\Big|_{\hat{\boldsymbol{\xi}}}$ is given by

$$\bigtriangledown \boldsymbol{g}(\hat{\boldsymbol{\xi}}) = \left[\frac{-2\hat{\boldsymbol{\delta}}\hat{\boldsymbol{\delta}}^\top\hat{\boldsymbol{V}}_\tau^{-1}}{1+\hat{\boldsymbol{\delta}}^\top\hat{\boldsymbol{V}}_\tau^{-1}\hat{\boldsymbol{\delta}}} + \frac{1}{1+\hat{\boldsymbol{\delta}}^\top\hat{\boldsymbol{V}}_\tau^{-1}\hat{\boldsymbol{\delta}}}\boldsymbol{I}_{(I-1)(J-1)} \quad \frac{\hat{\boldsymbol{\delta}}^\top\hat{\boldsymbol{V}}_\tau^{-1}\hat{\boldsymbol{\delta}}}{1+\hat{\boldsymbol{\delta}}^\top\hat{\boldsymbol{V}}_\tau^{-1}\hat{\boldsymbol{\delta}}}\boldsymbol{I}_{(I-1)(J-1)} + \frac{2\hat{\boldsymbol{\delta}}\hat{\boldsymbol{\delta}}^\top\hat{\boldsymbol{V}}_\tau^{-1}}{1+\hat{\boldsymbol{\delta}}^\top\hat{\boldsymbol{V}}_\tau^{-1}\hat{\boldsymbol{\delta}}}\right].$$

2 Estimates of Variance and Covariance Components for the Shrinkage Estimator

We compared model-based covariance estimates with empirical covariance estimates corresponding to the shrinkage estimator in a simulation study. The estimates for the off-diagonal entries in the dispersion matrix do not work uniformly well across simulation scenarios as the variance estimates of the diagonal entries of the same matrix. We noted that a much larger sample is required to obtain unbiased estimates of the covariance terms. Table 1 shows the simulation results of comparisons between empirical estimates and model-based estimates of the variances and covariances for the vector of shrinkage estimator (i.e., $\hat{\boldsymbol{\Sigma}}_{\hat{\boldsymbol{\tau}}_{shk}}$) under the same simulation settings as described in Section 6.1.

3 Empirical Distribution of the Shrinkage Estimator and the Approximate Wald Test Statistic

Though the limiting distribution of the shrinkage estimator is technically not normal, the simulation results reveal that this shrinkage estimator is approximately normal and the amount of departure from normality is small. Figure 1 shows the quantile-quantile plots of comparing the distribution of shrinkage estimator with the normal distribution (refer to Section 6.1 for simulation settings).

Figure 2 shows the quantile-quantile plots of comparing the distribution of $\tilde{T}_W$ with a χ^2 distribution, indicating that $\tilde{T}_W$ approximately follows a χ^2 with $df = (I-1)(J-1)$ under H_0. In fact, using the χ^2 null distribution would result in a slightly conservative test.

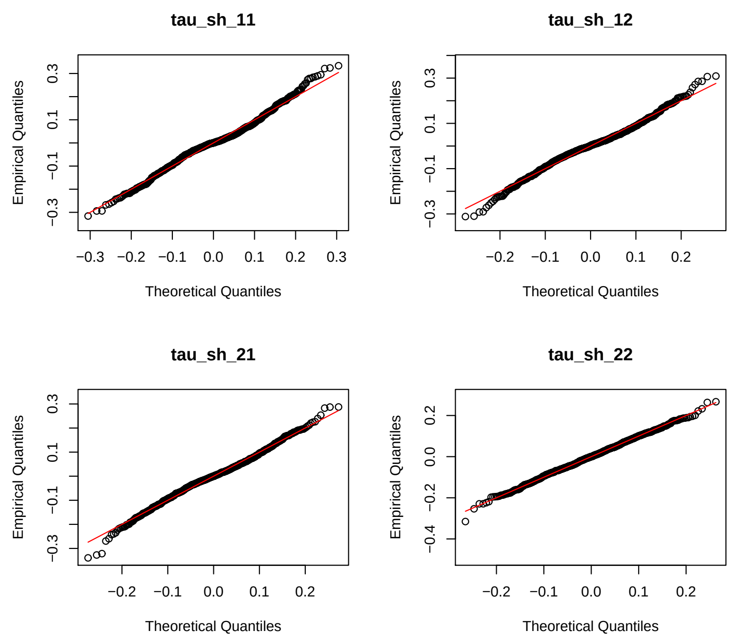

Figure 1: Quantile-Quantile (Q-Q) plots for comparing the distribution of the proposed shrinkage estimator with the normal distribution. The shrinkage estimates, $\hat{\boldsymbol{\tau}}_{shk} = (\hat{\tau}_{shk_{11}}, \hat{\tau}_{shk_{21}}, \hat{\tau}_{shk_{12}}, \hat{\tau}_{shk_{22}})^\top$, are obtained from the simulations of GEI in a 3×3 two-way table under H_0 of no interaction (N=1200 with repeated measures).

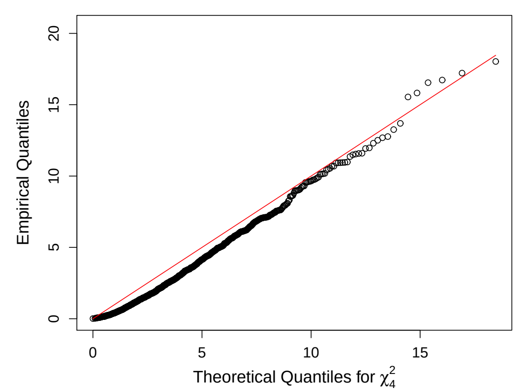

Figure 2: Quantile-Quantile (Q-Q) plot for comparing the distribution of the Wald statistics with the chi-squared distribution. The shrinkage estimates are obtained from the simulations of 3×3 GEI two-way table under H_0 of no interaction (N=1200 with repeated measures).

Table 1: Comparison between empirical and model-based estimates of variance and covariance components for the shrinkage estimator under Tukey's and saturated interaction structures in 3×3 table settings (N=1200 with repeated measures). Data were simulated under an autoregressive-1 correlation structure (see Section 6.1 for simulation details).

Simulation Model: Tukey's single degree of freedom

σ^2	Estimation	Variance				Covariance					
1	Empirical	0.0017	0.0013	0.0016	0.0014	-0.0006	-0.0001	0.0001	0.0001	-0.0001	-0.0005
1	Model-Based	0.0019	0.0014	0.0017	0.0012	-0.0007	-0.0003	0.0001	0.0001	-0.0003	-0.0006
4	Empirical	0.0070	0.0057	0.0069	0.0061	-0.0024	-0.0007	0.0008	0.0006	-0.0004	-0.0017
4	Model-Based	0.0078	0.0056	0.0069	0.0049	-0.0029	-0.0014	0.0005	0.0005	-0.0011	-0.0026
8	Empirical	0.0140	0.0113	0.0136	0.0111	-0.0044	-0.0017	0.0008	0.0016	-0.0009	-0.0038
8	Model-Based	0.0155	0.0112	0.0137	0.0097	-0.0057	-0.0027	0.0009	0.0009	-0.0021	-0.0051

Simulation Model: Saturated interaction

σ^2	Estimate	Variance				Covariance					
1	Empirical	0.0027	0.0021	0.0026	0.0019	-0.0010	-0.0005	0.0002	0.0002	-0.0004	-0.0010
1	Model-Based	0.0028	0.0021	0.0026	0.0019	-0.0010	-0.0005	0.0002	0.0002	-0.0004	-0.0010
4	Empirical	0.0104	0.0079	0.0087	0.0080	-0.0037	-0.0016	0.0009	0.0016	-0.0016	-0.0038
4	Model-Based	0.0101	0.0080	0.0097	0.0073	-0.0037	-0.0018	0.0006	0.0014	-0.0021	-0.0041
8	Empirical	0.0193	0.0162	0.0193	0.0158	-0.0079	-0.0037	0.0016	0.0034	-0.0035	-0.0073
8	Model-Based	0.0187	0.0151	0.0183	0.0136	-0.0068	-0.0034	0.0012	0.0029	-0.0041	-0.0078

4 Efficiency and Bias

Table 2 shows the bias and MSE for the interaction estimators $\hat{\boldsymbol{\tau}}$ from three models. We report only the results with $\rho = 0.5$ to save space. The results indicate that the linearization and IRGLS gives numerically consistent and unbiased parameter estimates for Tukey's one-df model. However, when the underlying interaction model is not a Tukey's model (e.g., AMMI1), Tukey's model yields severely biased estimates. In contrast, the saturated model has the least biased estimates. The performance of the proposed shrinkage estimator always lies between Tukey's and the saturated model.

Table 2: Mean squared error (MSE) and bias of interaction estimators from Tukey's one-df model, saturated interaction model, and the shrinkage method under different simulation models in 3×3 table settings (N=1200, see Section 6.1 for simulation setting details).

Simulation Model	True Parameter	$\sigma^2 = 4$						$\sigma^2 = 8$					
		Tukey		Shrinkage		Saturated		Tukey		Shrinkage		Saturated	
		MSE	Bias	MSE	Bias	MSE	Bias	MSE	Bias	MSE	Bias	MSE	Bias
Tukey	0.04	0.0004	-0.0045	0.0113	-0.0047	0.0070	-0.0047	0.0009	-0.0047	0.0226	-0.0103	0.0141	-0.0093
	0.07	0.0012	0.0015	0.0086	0.0010	0.0057	0.0012	0.0023	-0.0002	0.0171	0.0036	0.0113	0.0019
	0.07	0.0013	0.0012	0.0105	-0.0003	0.0069	0.0000	0.0026	0.0016	0.0205	0.0006	0.0136	0.0013
	0.14	0.0033	0.0032	0.0079	0.0042	0.0062	0.0039	0.0062	0.0024	0.0144	0.0040	0.0111	0.0040
AMMI1	0.14	0.0233	-0.1523	0.0113	0.0074	0.0101	-0.0044	0.0226	-0.1493	0.0231	0.0051	0.0195	-0.0130
	0.14	0.0271	-0.1634	0.0088	0.0073	0.0082	-0.0052	0.0261	-0.1579	0.0165	0.0066	0.0145	-0.0130
	-0.14	0.0105	0.0952	0.0098	-0.0018	0.0088	0.0052	0.0120	0.0929	0.0190	-0.0096	0.0156	0.0027
	-0.14	0.0075	0.0549	0.0069	-0.0071	0.0064	-0.0026	0.0125	0.0499	0.0160	-0.0074	0.0143	-0.0010
Saturated	0.00	0.0001	0.0030	0.0120	0.0027	0.0104	0.0026	0.0004	0.0056	0.0242	-0.0011	0.0193	-0.0006
	0.20	0.0390	-0.1958	0.0083	0.0002	0.0081	-0.0139	0.0382	-0.1916	0.0179	0.0048	0.0165	-0.0176
	0.20	0.0394	-0.1967	0.0091	0.0030	0.0088	-0.0115	0.0391	-0.1935	0.0218	0.0079	0.0195	-0.0145
	-0.20	0.0442	0.1983	0.0077	-0.0043	0.0081	0.0103	0.0484	0.1947	0.0157	-0.0066	0.0161	0.0160

5 Multivariate Shrinkage versus Scalar Shrinkage

We compared the shrinkage estimates of interaction parameters using only the diagonal elements of $\boldsymbol{B}$ versus using the whole $\boldsymbol{B}$ matrix (Table 3). Using scalar shrinkage (or so-called "component-wise shrinkage", the table shows the mean estimated weights $\hat{W}_{tuk}$ corresponding to $\hat{\boldsymbol{\tau}}_{tuk}$, $\hat{W}_{sat}$ corresponding to $\hat{\boldsymbol{\tau}}_{sat}$, and the resulting mean shrinkage estimator $\hat{\boldsymbol{\tau}}^{*}_{shk}$. We found that using the scalar version of $\boldsymbol{B}$, $\hat{\boldsymbol{\tau}}^{*}_{shk}$ is very close to $\hat{\boldsymbol{\tau}}_{shk}$ under Tukey's model since more weights are assigned to $\hat{\boldsymbol{\tau}}_{tuk}$ compared to $\hat{\boldsymbol{\tau}}_{sat}$. In fact, $\hat{\boldsymbol{\tau}}_{tuk} \approx \hat{\boldsymbol{\tau}}_{sat} \approx \hat{\boldsymbol{\tau}}_{shk} \approx \hat{\boldsymbol{\tau}}^{*}_{shk}$ under Tukey's model. However, this is not the case under AMMI1 or saturated interaction structures. In these cases, $\hat{W}_{tuk}$ dominates over $\hat{W}_{sat}$. As such, $\hat{\boldsymbol{\tau}}^{*}_{shk}$ is a biased estimate. The results indicate important contributions of the off-diagonal elements (covariances) of $\boldsymbol{B}$ and that multivariate shrinkage is required under certain situations.

Table 3: Parameter estimates using Tukey's model, the proposed adaptive shrinkage estimator, and saturated interaction models under Tukey's and saturated interaction structures in 3×3 table settings (N=1200 with repeated measures). Data were simulated under an autoregressive-1 (AR-1) correlation structure (see Section 6.1 for simulation details).

Model	True Parm.			Multivariate Shrinkage					Scalar Shrinkage		
		$\hat{E}[\hat{\boldsymbol{\tau}}_{tuk}]$	$\hat{E}[\hat{\boldsymbol{\tau}}_{sat}]$	$\hat{E}[\boldsymbol{B}]$				$\hat{E}[\hat{\boldsymbol{\tau}}_{shk}]$	$\hat{W}_{tuk}$	$\hat{W}_{sat}$	$\hat{E}[\hat{\boldsymbol{\tau}}^{*}_{shk}]$
	0.04	0.036	0.035	0.796	0.025	0.025	0.024	0.035	0.796	0.204	0.036
Tukey's	0.07	0.072	0.071	0.030	0.825	0.033	0.062	0.071	0.825	0.175	0.071
one df	0.07	0.071	0.070	0.028	0.031	0.822	0.064	0.070	0.822	0.178	0.070
	0.14	0.143	0.144	0.036	0.070	0.079	0.912	0.144	0.912	0.088	0.143
	0.14	-0.012	0.147	0.684	-0.314	0.107	0.105	0.136	0.684	0.316	0.059
AMMI1	0.14	-0.023	0.147	-0.254	0.591	0.126	0.118	0.135	0.591	0.409	0.064
	-0.14	-0.045	-0.142	0.153	0.206	0.881	-0.041	-0.135	0.881	0.119	-0.066
	-0.14	-0.085	-0.147	0.105	0.141	-0.019	0.931	-0.143	0.931	0.069	-0.094
	0.00	0.003	0.003	0.928	0.005	0.004	0.006	0.003	0.928	0.072	0.012
Saturated	0.20	0.004	0.200	-0.150	0.624	-0.168	0.215	0.186	0.624	0.376	0.092
Interaction	0.20	0.003	0.203	-0.156	-0.317	0.766	0.219	0.188	0.766	0.234	0.062
	-0.200	-0.002	-0.204	0.174	0.347	0.202	0.767	-0.190	0.767	0.233	-0.053

6 Additional Simulation Studies

Under the simulation setting described in Section 6.1, a simulation study was performed for cross-sectional studies ($n_k = 1$ for all k). The results, presented in Table 4, are similar to the longitudinal case.

For single GEI tests, we performed simulation studies using the same settings as Table 1 in the text with minor allele frequency = 0.1 and 0.2 respectively and increased the sample size to N = 6000 for a reasonable range of power (which is a reasonable sample size for investigating SNPs with smaller minor allele frequencies). The interaction effect sizes were adjusted accordingly to show the difference in power and type I error rates among the three tests. The results are displayed in Table 5. In general, the relative patterns are similar to Table 1 in the main text with increasing power for larger minor allele frequencies.

For multiple GEI tests, under the settings of Table 2 in the main text, we generated 100 SNPs with minor allele frequency $\sim$ Unif(0.1, 0.5) with N = 6000. The interaction effect sizes were also adjusted accordingly to show the difference in true positive and false positive rates among the three tests. The results are shown in Table 6. The upper panel of Table 6 shows the average performance of the three GEI tests for marginal models under scenario (A) where all 15 simulated GEI are of Tukey's form, scenario (B) where 2/3 of the simulated GEI are of Tukey's form, and scenario (C) where 2/3 of the interactions are of saturated forms. The lower panel of Table 6 shows the results of a multivariate model (single outcome) from 100 simulated SNPs. In conclusion, the GEI test using the shrinkage estimator has the most robust average performance with respect to various GEI structures compared to the tests using Tukey's and saturated interaction models.

Table 4: Power for detecting GEI and Type I error rates using Tukey's model, the proposed adaptive shrinkage estimator, and saturated interaction models under different interaction structures in 3×3 table cross-sectional study settings (N=1200)

	$\sigma^2 = 4$			$\sigma^2 = 8$		
Test Model / Simulation Model	Tukey LRT	Shrinkage Wald	Saturated LRT	Tukey LRT	Shrinkage Wald	Saturated LRT
Tukey's one-df	0.617	0.562	0.389	0.328	0.298	0.252
AMMI1	0.276	0.589	0.612	0.172	0.291	0.296
Saturated	0.038	0.510	0.638	0.092	0.252	0.354
$H_0 : \theta = 0$ (Additive)	0.047	0.045	0.054	0.046	0.047	0.052
$H_0 : \theta = 0$ (Null)	0.125	0.847	0.055	0.093	0.081	0.047

Table 5: Power for detecting GEI and Type I error rates using Tukey's model, the proposed adaptive shrinkage estimator, and saturated interaction models under different interaction structures in 3×3 table settings (N=6000). The minor allele frequency (MAF) was set at 0.1 and 0.2, respectively.

MAF = 0.1	$\sigma^2 = 4$			$\sigma^2 = 8$		
Test Model / True Model	Tukey LRT	Shrinkage Wald	Saturated LRT	Tukey LRT	Shrinkage Wald	Saturated LRT
Correctly Specified Correlation Structure (AR-1)						
Tukey's one-df	0.510	0.460	0.340	0.270	0.236	0.147
AMMI1	0.587	0.608	0.624	0.259	0.281	0.324
Saturated	0.463	0.619	0.679	0.174	0.285	0.359
$H_0 : \theta = 0$ (Additive)	0.058	0.039	0.052	0.057	0.041	0.050
$H_0 : \theta = 0$ (Null)	0.107	0.078	0.048	0.124	0.068	0.056
Misspecified Correlation Structure (Compound Symmetric)						
Tukey's one-df	0.481	0.392	0.256	0.253	0.213	0.144
AMMI1	0.352	0.443	0.482	0.254	0.265	0.289
Saturated	0.346	0.527	0.561	0.166	0.278	0.295
$H_0 : \theta = 0$ (Additive)	0.050	0.043	0.048	0.065	0.038	0.062
$H_0 : \theta = 0$ (Null)	0.106	0.066	0.054	0.118	0.067	0.064
MAF = 0.2	$\sigma^2 = 4$			$\sigma^2 = 8$		
Test Model / True Model	Tukey LRT	Shrinkage Wald	Saturated LRT	Tukey LRT	Shrinkage Wald	Saturated LRT
Correctly Specified Correlation Structure (AR-1)						
Tukey's one-df	0.937	0.931	0.868	0.670	0.569	0.432
AMMI1	0.823	0.910	0.927	0.584	0.619	0.652
Saturated	0.423	0.927	0.956	0.229	0.672	0.686
$H_0 : \theta = 0$ (Additive)	0.054	0.049	0.051	0.056	0.051	0.050
$H_0 : \theta = 0$ (Null)	0.098	0.063	0.054	0.151	0.108	0.053
Misspecified Correlation Structure (Compound Symmetric)						
Tukey's one-df	0.911	0.825	0.713	0.602	0.518	0.412
AMMI1	0.827	0.894	0.924	0.572	0.665	0.674
Saturated	0.462	0.898	0.925	0.151	0.658	0.665
$H_0 : \theta = 0$ (Additive)	0.042	0.049	0.053	0.065	0.042	0.062
$H_0 : \theta = 0$ (Null)	0.158	0.102	0.052	0.159	0.112	0.086

Table 6: Average performance of tests using Tukey's model, saturated interaction model, and the adaptive shrinkage estimator for detecting GEI across 100 simulated SNPs under scenarios (A): all simulated GEI are of Tukey's form, (B): 2/3 of simulated GEI are of Tukey's form and 1/3 are of saturated form, and (C): 2/3 of simulated GEI are of saturated form and 1/3 are of Tukey's form

Measure	Scenario	Tukey LRT	Shrinkage Wald	Saturated LRT
Marginal Models				
True Positive Rate	(A)	0.6975	0.6558	0.6417
	(B)	0.5629	0.6833	0.6482
	(C)	0.5345	0.6197	0.6523
False Positive Rate		0.0020	0.0006	0.0004
Multivariate Models				
True Positive Rate	(A)	0.3409	0.3213	0.1261
	(B)	0.3317	0.3044	0.1998
	(C)	0.1847	0.2248	0.2556
False Positive Rate		0.0041	0.0005	0.0004

Table 7: Baseline characteristics of 729 participants in the Normative Aging Study (NAS)

Variable	Mean ± SD, N (percent)
Pulse Pressure (mmHg)	54.26 ± 14.62
Age (years)	66.37 ± 7.12
Body Mass Index (kg/m^2)	27.97 ± 3.77
Race (white)	705 (97%)
Type-2 Diabetes	95 (13%)
Hypertension	397 (54%)
Pack-Years of Cigarette Smoking	
0	226 (31%)
< 30	283 (40%)
≥ 30	206 (29%)
Cumulative Lead Exposure (μg/g): Tibia Bone	
$\leq$15	259 (36%)
(15,25]	263 (36%)
$>$25	207 (28%)
Cumulative Lead Exposure (μg/g): Patella Bone	
$\leq$20	244 (33%)
(20,32]	223 (31%)
$>$32	262 (36%)
Number of Repeated Measures on Pulse Pressure Per Subject	
1–2	147 (20%)
3–4	236 (32%)
5–6	286 (39%)
7–8	60 (9%)

Table 8: Baseline characteristics of 6361 participants in the Multi-Ethnic Study of Atherosclerosis (MESA)

	Caucasian (N=2526)	Chinese (N=775)	African American (N=1611)	Hispanic (N=1449)
Age (years)	62.66 ± 10.24	62.38 ± 10.38	62.29 ± 10.06	61.38 ± 10.30
Body Mass Index (kg/m^2)	27.74 ± 5.06	23.99 ± 3.29	30.15 ± 5.89	29.45 ± 5.14
Gender (female)	1320 (52%)	394 (51%)	868 (54%)	910 (62%)
Education (college and above)	1522 (60%)	392 (51%)	772 (48%)	312 (22%)
Total Gross Family Income ($\geq$ 50,000)	1397 (55%)	218 (28%)	554 (37%)	104 (7%)
Energy Intake (kcal/day)				
$\leq$ 1000	511 (22%)	360 (47%)	429 (17%)	315 (24%)
(1000, 1300]	486 (20%)	174 (23%)	354 (14%)	250 (19%)
(1300, 1600]	437 (18%)	91 (12%)	383 (15%)	210 (16%)
(1600, 2000]	435 (18%)	76 (10%)	502 (20%)	209 (16%)
>2000	512 (22%)	61 (8%)	851 (34%)	339 (26%)
Total Intentional Exercise (minute/week)				
$\leq$ 0	429 (17%)	197 (25%)	364 (27%)	448 (31%)
(0, 420]	354 (14%)	123 (16%)	252 (18%)	190 (13%)
(420, 840]	383 (15%)	122 (16%)	220 (16%)	230 (16%)
(840, 1680]	502 (20%)	166 (21%)	207 (15%)	225 (16%)
>1680	851 (34%)	331 (24%)	331 (24%)	355 (25%)
Number of Repeated Measures on BMI Per Subject				
1	104 (4%)	69 (9%)	128 (8%)	141 (10%)
2	107 (4%)	32 (4%)	103 (6%)	90 (6%)
3	154 (6%)	38 (5%)	125 (8%)	35 (2%)
4	2161 (86%)	636 (82%)	1255 (88%)	1183 (82%)

Table 9: BMI-associated single-nucleotide polymorphisms (SNPs) with significant meta-analysis p-values for GEI tests in the MESA data (adjusted $\alpha = 0.0019$) for the four race groups (*** denotes $p < 1 \times 10^{-8}$).

			Caucasian			Chinese			African American			Hispanic		
			Tuk	Shk	Sat	Tuk	Shk	Sat	Tuk	Shk	Sat	Tuk	Shk	Sat
Exposure	SNP ID	Gene	LRT	Wald	LRT	LRT	Wald	LRT	LRT	Wald	LRT	LRT	Wald	LRT
Energy	rs2815752	NEGR1	0.607	0.993	0.949	0.009	0.032	0.319	0.198	0.500	0.590	0.665	0.997	0.967
Intake	rs543874	SEC16B	0.115	0.441	0.309	NA	NA	NA	NA	NA	0.554	***	***	***
	rs2867125	TMEM18	0.239	0.462	0.281	0.529	0.963	0.841	0.350	0.717	0.495	NA	NA	0.314
	rs987237	TFAP2B	0.286	0.370	0.214	0.090	0.399	0.436	0.206	0.455	0.644	0.853	1.000	0.989
	rs3817334	MTCH2	0.108	0.189	0.093	0.028	0.121	0.418	0.017	0.093	0.423	0.629	0.992	0.941
	rs3810291	TMEM160	0.562	0.617	0.360	NA	NA	0.509	NA	NA	0.021	0.997	0.930	0.721
Intentional	rs543874	SEC16B	NA	NA	0.117	0.002	0.014	0.057	NA	NA	0.259	0.005	0.039	0.121
Exercise	rs1514175	TNNI3K	NA	NA	0.793	0.238	0.711	0.829	NA	NA	0.800	0.055	0.147	0.104
	r10938397	GNPDA2	0.133	0.357	0.255	0.031	0.293	0.585	0.022	0.217	0.185	NA	NA	0.170
	rs7359397	SH2B1	0.747	0.104	0.037	0.017	0.203	0.240	NA	NA	0.536	0.715	0.698	0.424