Estimation of genomic prediction accuracy from reference populations with varying degrees of relationship

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Running title: Estimation of genomic prediction accuracy

Key words: Genomic prediction; Prediction accuracy; Effective number of chromosome segments; Genomic prediction design; varying degrees of relationship

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ABSTRACT

Genomic prediction is emerging in a wide range of fields including animal and plant breeding, risk prediction in human precision medicine and forensic. It is desirable to establish a theoretical framework for genomic prediction accuracy when the reference data consists of information sources with varying degrees of relationship to the target individuals. A reference set can contain both close and distant relatives as well as 'unrelated' individuals from the wider population in the genomic prediction. The various sources of information were modeled as different populations with different effective population sizes (N_e). Both the effective number of chromosome segments (M_e) and N_e are considered to be a function of the data used for prediction. We validate our theory with analyses of simulated as well as real data, and illustrate that the variation in genomic relationships with the target is a predictor of the information content of the reference set. With a similar amount of data available for each source, we show that close relatives can have a substantially larger effect on genomic prediction accuracy than lesser related individuals. We also illustrate that when prediction relies on closer relatives, there is less improvement in prediction accuracy with an increase in training data or marker panel density. We release software that can estimate the expected prediction accuracy and power when combining different reference sources with various degrees of relationship to the target, which is useful when planning genomic prediction (before or after collecting data) in animal, plant and human genetics.

INTRODUCTION

Genomic prediction of (additive) genetic effects and phenotypes is emerging in a wide range of fields including animal and plant breeding, risk prediction in human medicine and forensics[1-4]. Genomic prediction requires modeling of the association between genome-wide single nucleotide polymorphisms (SNPs) and phenotypes. The success of genomic prediction is measured by its accuracy, i.e. how reliable a future phenotype of target individuals can be predicted.

Genomic prediction requires a reference population of individuals having information on both genotype and phenotype. The accuracy of genomic prediction depends on various parameters, including sample size of the reference and its genetic structure. An important parameter in relation to the latter is the effective size of the population. The effective population size is a predictor of the effective number of chromosome segments that are represented in the population[5-7]. Theoretical predictions have usually considered a homogeneous population of individuals that are essentially unrelated. However, in most practical applications, the reference population used for genomic predictions possibly consists of many sub-groups with individuals having a variety of relatedness to the target individual, e.g. direct relatives, more distant relatives, and individuals that are considered unrelated. It is relevant to assess the contribution of these various sources to prediction accuracy before actually conducting an experiment.

A number of studies have shown that genomic predictions are more accurate if the genomic relationship between the proband and the reference population is higher, both in humans[8-11] and in other species[12-14]. Habier et al (2013)[15]

distinguished between three types of information in genomic prediction; linkage disequilibrium, additive-genetic relationships and co-segregation of QTL predicted from markers genotypes with a pedigree. They argued that it would be useful to understand how these sources contribute to the accuracy of genomic predictions, especially when designing reference populations for breeding programs. They show these contributions via simulated examples but did not provide methods that allow simple predictions for their contribution to accuracy. Pszczola et al. (2012)[16] showed that the relationship between the reference population and the proband should be maximized to achieve an optimal design using a simulation study. However, they also did not attempt to derive the expected prediction accuracy from an optimal design in advance. Hayes et al. (2009)[17] considered the influence of direct relatives on genomic prediction. They followed the same approach as the general theory, i.e. by considering the number of independently segregating chromosome segments within families. They showed the accuracy of genomic prediction from varying sizes of the first and second degree of relatives, but did not consider the information from combined sources[18]. It should also be noted that those studies that derived genomic prediction accuracy from theory using effective number of chromosome segments (M_e)[5, 6, 19-21], did not consider the correlation between relatedness at different chromosomes, therefore overestimating M_e and underestimating whole-genome prediction accuracy[7].

Wientjes et al (2016)[22] proposed a simple selection index approach to combine information from different populations. They considered a genetic correlation between genetic effects expressed in different populations. We propose to use the same approach to combine different sources of information from different subsets

97 within a population, where the different subsets have a different degree of relationship
98 with the target individual. To predict the accuracy, we derive the number of effective
99 chromosome segments from a hypothetical N_e associated with each subset, and we
100 show that that combining such subsets using selection index theory gives the same
101 result as using a prediction from an M_e derived from the variation in genomic
102 relationships between the overall reference data and the target. Prediction accuracy is
103 derived from variation in genomic relationship rather than the variation in genomic
104 relationship as a deviation for the expected relationship among members of the
105 reference set, as was proposed by Goddard et al (2011) and also applied by Wientjes
106 et al (2016). This approach leads to a theoretical concept useful for assessing the
107 accuracy of genomic predictions in advance, and we illustrate this with examples
108 based on real data.

MATERIALS AND METHODS

Predicting genomic selection accuracy

The accuracy of genomic breeding values (GBV) or (genomic profile score in the context of human risk prediction[23]) based on genome-wide SNP genotypes can be predicted from theory[5-7, 24], assuming that prediction is based on a reference population with phenotypes and genotypes for the same genome-wide SNPs that are linked to quantitative trait loci (QTL). The accuracy depends on i) the proportion of genetic variance at QTL captured by markers and ii) the accuracy of estimating marker effects. The proportion of genetic variance at QTL captured by markers (b) depends on linkage disequilibrium (LD) between markers and QTL, which in turn depends on the number of markers (M) and the number of 'effective chromosome segments' (M_e)[5], that is

b = M / (M_e + M)[5].

Various forms of prediction of M_e have been presented[5, 6, 21] that were however inconsistent to each other, and without considering the correlation between chromosomes. Recently, we presented a prediction formula with the form[7]

$$M_e = \frac{N_{chr}}{[\ln(2N_eL+1)+2N_eL(\ln(2N_eL+1)-1)]/(4N_e^2L^2)+(1/3N_e)\cdot(N_{chr}-1)} \quad (1)$$

where N_e = effective population size; L = average chromosome length; N_{chr} = number of chromosomes. This formula accounts for mutation, and that without considering mutation should be referred to equation (10) in Lee et al. (2017)[7]. If N_{chr} = 30 and L = 1, Eq. (1) can be approximately simplified as

$$M_e = 2.938\ N_e^{0.965}, \text{ and } N_e = 0.327\ M_e^{1.036}. \quad (2)$$

The accuracy of the genomic prediction of a phenotype can be written as[5]

$$r_{y,\hat{g}} = h \cdot r_{g,\hat{g}} = h \cdot \sqrt{\frac{bh^2}{bh^2 + M_e / N}} = \sqrt{\frac{bh^4}{bh^2 + M_e / N}} \quad (3)$$

where $r_{y,\hat{g}}$ is the correlation coefficient between the true phenotypes (y) and estimated GBV, h^2 is the heritability of the trait, and N is the number of phenotypic observations. Other measures for genomic prediction accuracy, particularly for human risk prediction, such as the area under the receiver operating characteristic curve (AUC) or odds ratio of case-control status contrasting the higher or lower risk group are described elsewhere[7].

M_e and genomic relationship

After collecting genotypic information of the reference data and the target individual, it is possible to obtain an empirical M_e from a genomic relationship matrix (GRM). The elements in the GRM are $G_{Tj} = \sum_{m=1}^{M} x_{Tm} x_{jm} / M$ where x_{Tm} and x_{jm} are the standardised genotype coefficients (mean 0 and variance 1) for the target individual (T) and jth individual in the reference data at the mth locus. It is possible to construct a GRM for each locus, and the elements in the GRM at the mth locus are $G_{Tj(m)} = x_{Tm} x_{jm}$. Then, the variance of the mean of $G_{Tj(m)}$ across all M_i SNPs in a single chromosome is

$$\begin{aligned}
\mathrm{var}\left(\sum_{m=1}^{M_i} G_{Tj(m)} / M_i\right) &= \frac{1}{M_i^2}\left[\sum_{m=1}^{M_i}\sum_{l=1}^{M_i} \mathrm{cov}(G_{Tj(l)}, G_{Tj(m)})\right] \\
&= \frac{1}{M_i^2}\left[\sum_{m=1}^{M_i}\sum_{l=1}^{M_i} \mathrm{cov}(x_{T(l)} x_{j(l)}, x_{T(m)} x_{j(m)})\right] \\
&= \frac{1}{M_i^2}\left[\sum_{m=1}^{M_i}\sum_{l=1}^{M_i} \mathrm{cov}(x_{j(l)}, x_{j(m)})\mathrm{cov}(x_{T(l)}, x_{T(m)})\right] \\
&= \frac{1}{M_i^2}\left[\sum_{m=1}^{M_i}\sum_{l=1}^{M_i} r_{m,l}^2\right] \\
&= \frac{1}{M_{e(i)}}
\end{aligned} \tag{4}$$

150 where $\mathrm{cov}(x_{j(l)}, x_{j(m)}) = \mathrm{cov}(x_{T(l)}, x_{T(m)}) = r_{m,l}$, which is a correlation between the mth

151 and l^{th} SNP-genotype, because of var(x) = 1 and mean(x) = 0, i.e. the genotype

152 coefficients are standardized in the population. The term $M_{e(i)}$ is the effective number

153 of chromosome segments for the ith chromosome, and it is calculated from the

154 inverse of the average of the squared correlation between the M_i SNPs[6, 7]. When

155 considering multiple chromosomes, the covariance of the pairwise relationship

156 between two chromosomes is not negligible[7]. Assuming equal length and number of

157 SNPs for N_{chr} chromosomes, M_e for the whole genome can be derived from the

158 variance in the relationship across the whole genome as

159 $$\frac{1}{M_e} = \left[\mathrm{var}\left(\sum_{m=1}^{M_i} G_{Tj(m)} / M_i \right) + \left(\frac{N_{chr} - 1}{3N_e} \right) \right] \cdot \frac{1}{N_{chr}} = \mathrm{var}\left(\sum_{m=1}^{M} G_{Tj(m)} / M \right) = \mathrm{var}(G_{Tj}) \qquad (5)$$

160 where N_{chr} is the number of chromosomes. This expression is equivalent to (1) when

161 using Sved (1971)[25] for deriving the expected squared correlation between

162 genotypes, which is dependent on N_e. An empirical M_e can be derived from the GRM

163 as the variance in relationships between a target individual T and N individuals in the

164 reference population. Goddard et al. (2011)[5] suggested their theoretical derivation had

165 to assume a homogeneous population of individuals that are essentially unrelated.

166 However, Eq. (4) show that the assumption about unrelated individuals is not

167 necessary so that any random samples from the population can be used, irrespective

168 of whether they are highly related or not (see Results).

169

170 **Effective population size in a reference data set**

171 One of critical parameters to determine the accuracy of genomic prediction is the

172 effective population size (N_e). It is not very common to represent a reference

173 population by a single value of N_e when it consists of several cohorts of individuals

with different relationships to the target individual. Wientjes et al. (2016)[22] used a single value for M_e representing a reference set consisting of two populations. Here, we generalized that concept for any number of subsets of the reference population based on the relationship between N_e, M_e and var(G_{T*}), leading to a certain value for M_e and N_e for a reference population consisting of several cohorts. For any subset of the reference data set, there are realized relationships with the target sample. From Eq. (5), a value of M_e, which is the inverse of the variance of the genomic relationships between the target and the reference sample, can be assigned to the reference data. Then, a single value of N_e, which is a function of M_e from Eq. (1) or (2), can be obtained for the reference data. The effective population size of the reference set is therefore a parameter specific to the data used and it describes genomic diversity of the reference individuals used for prediction of genomic breeding value relative to the target individual which breeding value is being predicted. This N_e value can be smaller than the effective size of the population from which the reference individuals were sampled, but it can also be larger, depending on whether the reference individuals chosen were closer or more distantly related to the reference set.

Based on this concept of N_e, reflecting information content of the reference sample in relation to the target sample, we consider three information sources consisting of i) close relatives of the proband, e.g. N_e = 10, ii) distant relatives or individuals from the local area of the proband, e.g. N_e = 100 and iii) a wider population sample of individuals that are not related to the proband, e.g. N_e = 1,000.

The GBV can be estimated based on each of these information sources, and the accuracy of the estimation can be calculated as above, e.g. $r_{g,\hat{g}(i)}$ from Eq. (3) where i represents the ith information source. It is also possible to estimate GBV based on combined data of all three information sources. Assuming a random sample from the same population for each source, the accuracy of the GBV based on the combined data set can then be calculated using standard selection index theory as

$$r_{g,\hat{g}} = \sqrt{\mathbf{g}'\mathbf{P}^{-1}\mathbf{g}} = \sqrt{\begin{bmatrix} r^2_{g,\hat{g}(1)} \\ r^2_{g,\hat{g}(2)} \\ r^2_{g,\hat{g}(3)} \end{bmatrix}' \begin{bmatrix} r^2_{g,\hat{g}(1)} & r^2_{g,\hat{g}(1)} \cdot r^2_{g,\hat{g}(2)} & r^2_{g,\hat{g}(1)} \cdot r^2_{g,\hat{g}(3)} \\ r^2_{g,\hat{g}(2)} \cdot r^2_{g,\hat{g}(1)} & r^2_{g,\hat{g}(2)} & r^2_{g,\hat{g}(2)} \cdot r^2_{g,\hat{g}(3)} \\ r^2_{g,\hat{g}(3)} \cdot r^2_{g,\hat{g}(1)} & r^2_{g,\hat{g}(3)} \cdot r^2_{g,\hat{g}(2)} & r^2_{g,\hat{g}(3)} \end{bmatrix}^{-1} \begin{bmatrix} r^2_{g,\hat{g}(1)} \\ r^2_{g,\hat{g}(2)} \\ r^2_{g,\hat{g}(3)} \end{bmatrix}} \quad (6)$$

where **g** is the vector with covariances between each of the GBV and the true breeding value, and **P** is the variance-covariance matrix of the set of GBV. The accuracy of the GBV based on the combined data set can also be estimated based on the weighted M_e from the three information sources. Assuming a random sample from the same population for each source, the weighted M_e can be obtained as

$$M_{e(weighted)} = \frac{1}{\sum_{k=1}^{N_{sub-sample}} \mathrm{var}(G_{Tj})_k \, p_k} = \frac{1}{\sum_{k=1}^{N_{sub-sample}} \frac{p_k}{M_{e(k)}}} \quad (7)$$

where p_k is the proportion of the sample size over the total sample for each information source. The accuracy of the GBV based on the weighted M_e is identical with that using standard selection index theory above (Eq. (6)).

Following Wientjes et al. (2016)[22] we can further generalize for a case where genetic correlations among multiple reference populations and those between reference populations and the target are not one. Equation (6) can be generalized as

$$r_{g,\hat{g}} = \sqrt{\mathbf{g}'\mathbf{P}^{-1}\mathbf{g}} = \sqrt{\begin{bmatrix} r^2_{G_{1,T}} r^2_{g,\hat{g}(1)} \\ \vdots \\ r^2_{G_{k,T}} r^2_{g,\hat{g}(k)} \end{bmatrix}' \begin{bmatrix} r^2_{G_{1,T}} r^2_{g,\hat{g}(1)} & \cdots & r^2_{g,\hat{g}(1)} r^2_{g,\hat{g}(k)} r_{G_{1,k}} r_{G_{1,T}} r_{G_{k,T}} \\ \vdots & \ddots & \vdots \\ r^2_{g,\hat{g}(k)} r^2_{g,\hat{g}(1)} r_{G_{k,1}} r_{G_{k,T}} r_{G_{1,T}} & \cdots & r^2_{G_{k,T}} r^2_{g,\hat{g}(k)} \end{bmatrix}^{-1} \begin{bmatrix} r^2_{G_{1,T}} r^2_{g,\hat{g}(1)} \\ \vdots \\ r^2_{G_{k,T}} r^2_{g,\hat{g}(k)} \end{bmatrix}} \quad (8)$$

where $r_{G_{k,T}}$ is the genetic correlation between the kth reference population and the target set, and similarly, $r_{G_{i,j}}$ is the genetic correlation between the ith and j^{th} reference population ($i = j = 1 \sim k$).

Equation (8) can be used when multiple reference populations have both quantitative traits and diseases. If the kth reference population is measured for binary response (disease or disorder), the reliability term, $r^2_{g,\hat{g}}$, in Eq. (8) can be replaced with

$$r^2_{u,\hat{u}} = \frac{h^2 z^2}{h^2 z^2 + [K(1-K)]^2 \cdot M_e / [P(1-P) \cdot N]}$$

where u is a genetic profile score on the 0,1 disease scale[26, 27], K is the population prevalence for the disease, P is the proportion of cases in the total sample N of cases and controls, and z is the density at the threshold on the normal distribution in the liability threshold model.

When the target data set is measured for a binary response (e.g. diseases), the AUC or odds ratio of case-control status contrasting the higher or lower risk group can be also estimated[7]. These measures for genomic prediction accuracy with multiple heterogeneous reference populations can be obtained using MTG2, publicly available software (https://sites.google.com/site/honglee0707/mtg2).

Power of genomic prediction

The power depends on the sample size in the target data set and the overall reliability of the genomic prediction (Eq. (8)).

$$NCP = N_T \cdot r^2_{y,\hat{g}} / (1 - r^2_{y,\hat{g}})$$

where NCP is the non-centrality parameters, N_T is the sample size in the target data and $r^2_{y,\hat{g}}$ is the coefficient of determination of the predictor. Then, the power can be written as

242 $$power = 1 - \Phi\left[\Phi^{-1}(1-\alpha/2) - \sqrt{NCP}\right] + \Phi\left[\Phi^{-1}(\alpha/2) - \sqrt{NCP}\right]$$

243 where Φ is the cumulative standard normal function and α is the significance level.
244 When using the odds ratio of case-control status contrasting the higher or lower risk
245 group, the non-centrality parameters can be derived as[28]

246 $$NCP = \ln(OR)^2\left[N_{top}P_{top}(1-P_{top})P_{bottom}(1-P_{bottom})\right] / \left[P_{bottom}(1-P_{bottom}) + (N_{top}/N_{bottom})P_{top}(1-P_{top})\right]$$

247 where N_{top} and N_{bottom} is the number of individuals in the top and bottom percentile,
248 and P_{top} and P_{bottom} is the proportion of cases in each group. The power can be
249 estimated as above.
250

251 **Simulation**

252 In a simulation, a stochastic gene-dropping method [29, 30] was used to simulate
253 4,000 SNPs for each of 30 chromosomes, each of length L=1 Morgan with N_e = 50,
254 500 and 1000 for 50, 500 and 1000 generations, respectively. Recombination and
255 mutations were modelled according to the genetic distance between SNPs and the
256 mutation rate of 1e-08 per site per generation[31]. In the final generation, we
257 constructed a genomic relationship matrix for a random set of 3000 individuals.
258 Among the 3000 individuals, we randomly selected 1000 individuals as target data
259 and 2000 individual as reference data, and estimated variance of the genomic
260 relationships between the target and reference data to validate Eq. (1), (2), (4) and (5).
261

262 **Evaluation of the formulas**

263 For each of the three information sources contributing to genomic prediction we
264 varied values for N_e, sample size in reference data and marker density. We compared
265 the expected accuracy of GBV from the sample of N_e =1000 with predictions that

266 additionally included information from the sample of N_e =100 and N_e =10. The total
267 number in the reference population was kept equal between the comparisons.
268
269 **Real data analysis**
270 We used publicly available data from the Framingham heart study
271 (phs000007.v26.p10.c1)[32]. There were 6950 individuals genotyped for 500,568
272 SNPs. Stringent quality control for genotype data and phenotype adjustment for
273 confounders were applied to the data (the details can be found in Lee et al. (2016)[7]).
274 The quality control included SNP call rate > 0.95, individual call rate > 0.95, HWE p-
275 value > 0.0001, MAF > 0.01 and individual population outliers < 6 SD from the first
276 and second principal components (PC). After QC, 6920 individuals and 389,265
277 SNPs remained. Among them, 4243 individuals were phenotyped for height and body
278 mass index (BMI).

279 We made three different information sources to form the reference data that were
280 tested in 100 replicated analyses (Table 1). Initially, we randomly selected 800
281 individuals out of 4243 phenotyped individuals as a target data set. For reference data
282 set #1, we selected 50% of individuals that were highly related (> relatedness of 0.3)
283 to the 800 target individuals (N_1 = 617 ± 19). For reference data set #2, we selected
284 80% of moderately related individuals (> relatedness of 0.1) of the 800 target
285 individuals (N_2 = 1254 ± 30). For reference data set #3, we took the rest of the
286 individuals that were not selected for reference data set #1 and #2 (N_3 = 1572 ± 33).
287 There was no overlap sample between target data set and reference data sets #1, #2
288 and #3.

289 Using the real genotype data, the genomic relationships between the reference and
290 target sample were constructed. Empirical M_e was estimated from equation (5) for

291 reference #1, 2 and 3, and that for combined data. We took a median rather than mean
292 because the distribution of variance of the genomic relationship between target and
293 reference sample was skewed. The correlation between the true phenotypes (that were
294 not used in the analyses) and estimated GBV in the target data set was estimated for
295 the combined data set, which was used as the genomic prediction accuracy ($r_{y,\hat{g}}$).
296 Phenotypes were adjusted for birth year, sex, and the first 10 PCs were used to control
297 non-genetic confounding effects, e.g. population stratification.

298

299 **RESULTS**

300 In the simulation study, as shown in Figure 1A, 1B and 1C, the expected (from Eq.
301 (1)) and empirically observed M_e from the simulated genotyped data (using Eq. (5))
302 are in good agreement, however, they are considerably lower than the expectation
303 from the previous formulas[5, 6, 21], which confirms the result from Lee et al.
304 (2017)[7]. It is noted that Eq. (5) is still valid in the subset with a smaller N_e = 50 that
305 has a significant proportion of high related individuals, indicating that the assumption
306 about unrelated individuals (made in Godard et al. (2011)[5]) can be relaxed. It is
307 shown that whether using a high or low effective population size, the mean and
308 variance of genomic relationships is generally agreed with the expectation from the
309 theory (Supplementary Figures S1 and S2).

310

311 In the evaluation of the formulas, we first tested how the prediction accuracy was
312 changed with varying marker density, using formula (1) and (3) and b = M / (M_e + M)
313 (Figure 2). For N_e=10,000, the accuracy gradually increased with marker density, but
314 the slope became flat when using the number of SNPs exceeded 100,000 (Figure 2A).

315 For N_e=1,000, the accuracy did not increase with marker density as long as the
316 number of SNPs was higher than 50,000 (Figure 2B). For N_e=100, there was no
317 improvement of the accuracy if the number of SNPs was more than 10,000 (Figure
318 2C). This would be expected because the proportion of genetic variance at QTL
319 captured by markers ($b = M / (M_e + M)$) approached one when the number of SNPs
320 (M) was more than 100,000, 50,000 and 10,000 for N_e = 10,000, 1000 and 100,
321 respectively (Figure 3), as M_e was equal to 21,248, 2,313 and 254 for these three
322 cases.
323
324 Next, we quantified the contribution of each information source when varying sample
325 size in the reference data using formula (1), (3) and (5) (Figure 4). It was assumed
326 that the number of SNPs was sufficient to capture most of causal variants (e.g. >
327 50,000). When adding 100 individuals of N_e=100 or N_e=10 to the reference sample
328 with N_e=1000, the accuracy was slightly or substantially improved (Figure 4A). The
329 improvement was larger when adding more individuals (500) (Figure 4B). Results
330 showed that an information source of a smaller N_e was more important when the
331 samples sizes of each information source were the same. When the total number of
332 reference data was increased, the importance of adding an information source of a
333 smaller N_e was relatively decreased (Figure 4). When heritability was higher, overall
334 accuracy was increased, and the relative contribution from an information source of a
335 smaller N_e, i.e. the close relatives, was reduced (Figure 5).
336
337 Figure 6 confirms again that the smaller N_e, the better the prediction accuracy when
338 using each information source separately. However, the sample sizes can be also
339 varied across the information sources, as there are generally a lot fewer close relatives

340 than individuals from the wider population. In Figure 6A, the accuracy at a sample
341 size of 100 for N_e=10 was 0.73, which was lower than that of a sample size of 1,000
342 for N_e=100 (0.81) or that of a sample size of 20,000 for N_e=1,000 (0.83). With a
343 higher heritability, the result is similar in that the 20,000 records in the information
344 source of N_e=1000 gave a better accuracy than the 100 records of close relatives
345 (N_e=10).
346
347 In real situations, the most common and desirable design may combine all of the
348 information sources to maximize the prediction accuracy. We plotted the accuracy
349 using a composite design consisting of N_e=1000 + N_e=100 (N=500) + N_e=10 (N=50),
350 compared to that using N_e=1000 (Figure 7). The accuracy for a composite design was
351 substantially increased especially when the total number of reference sample is low
352 (Figure 7).
353
354 Figure 8 illustrates the real data analyses. The median of empirically estimated M_e
355 from the inverse of the variance of the genomic relationship (Eq. 5) over 100
356 replicates was 2254 (SD=50), 3989 (SD=104) and 28848 (SD=920) for reference #1,
357 #2 and #3, respectively (Table 1). Empirically estimated M_e based on the combined
358 data was 4836 (SD=106) while expected M_e was 5309 (SD=88), approximately
359 confirming Eq. (7). The (small) difference between empirical observation and
360 expectation was probably due to skewed distribution of the variance of the genomic
361 relationships.
362
363 Given M_e, N and h^2, the expected accuracy agreed well with the observed accuracy
364 when using Framingham data (Figure 9). The reported heritabilities, h^2=0.8 [33-35]

365 for height and h^2=0.46[36, 37] for BMI, were used. We also quantified the importance
366 of marker density using the real data. In agreement with Figure 2, the prediction
367 accuracy is not much decreased even with 50,000 SNPs that were randomly selected
368 from 389,265 SNPs (Figure 10).
369
370
371 **DISCUSSION**
372 This work shows a simple approach for modeling genomic prediction in a reference
373 data set that contained several subpopulations that differ in relatedness to the target
374 set, and by modeling these subpopulations as having different effective population
375 size. The model allows assessing the prediction accuracy before actually conducting
376 an experiment so that designing genomic prediction can be precise and effective in
377 animal, plant and human genetics. For example, it can address a question how much
378 the prediction accuracy can be increased by adding 10,000 (conventionally) unrelated
379 individuals into the current experiment consisting of 100 relatives in the reference
380 data. The value for N_e in equation (1) can be approximated based on prior knowledge
381 of a population, and the relatedness of the sample with the target, possibly supported
382 by some genotype information that maybe available on cohorts, or samples thereof.
383 As a reference table, we added approximated value of N_e for structured population of
384 full and half sibs (Supplementary Tables 1 and 2). Prediction in advance indeed relies
385 on arbitrary modelling a number of cohorts, but it would be a useful exercise, as
386 illustrated in the results when considering marker density and various sizes of the
387 subsets of the training data. The theory is also useful for an animal breeder to predict
388 the value of genotyped animals in an own herd versus those in a wider references
389 population consisting of a larger number of more distantly related individuals.

390

391 The genotypic and phenotypic information of close and distant relatives of the
392 proband can be effectively used as a part of the unified reference panel that also
393 include a large number of individuals that are not related to the predicted subject to
394 improve the accuracy further as illustrated in Figure 7. For a random sample from the
395 same homogenous population, e.g. within the same breed or ethnicity, an optimal
396 design should consist of both close and distant relatives and unrelated individuals, e.g.
397 a composite design, to maximise the prediction accuracy (Figure 7). That is, the
398 composite design takes advantage of effective information from smaller number of
399 relatives while it also use information from a greater number of unrelated individual.
400

401 We showed that the prediction accuracy derived for a population with unrelated
402 individuals turns out to be higher, compared to previous quantifications that
403 overestimated M_e for a larger number of chromosomes[5, 6, 21, 38]. Using the same
404 theory, we also showed that the information from close relatives could increase the
405 accuracy even further, especially for smaller reference populations (Figures 3 – 6). It
406 is important to note that the assumption about using unrelated individuals in
407 estimating empirical M_e from genomic relationship[5] is not strictly necessary and can
408 be relaxed (Eq. (4) and (5)). The theory and empirical observation from simulation
409 study agreed well (Figure 1) even when using a population with a smaller effective
410 population size (N_e=50) that consisted of a significant proportion of high relatedness.
411

412 Previous studies related to genomic prediction accuracy have suggested that M_e can
413 be derived from the variation in the differences between realized and expected
414 relationships[6, 22], i.e. **D** = **G** – **A** where **G** is a genomic relationship matrix and **A** is

415 a numerator relationship matrix based on pedigree. Those studies validated their
416 results also with simulation. If the individuals used in the training set have a low
417 expected relationship to the target individuals, then there is not much difference
418 between the variations in **D** versus **G**. However, when some closer relatives are used,
419 var(**G**) is larger than var(**D**) and M_e is therefore smaller. Note that non-random
420 sampling of individuals used for the training set can cause a difference between the N_e
421 of the population that was simulated, and the N_e of the data set that was used for
422 prediction.
423
424 We have not tested the theory for multi-breed reference populations, i.e. those that are
425 heterogeneous in the sense of consisting of populations from different genetic
426 background, i.e. different breeds or ethnicities, each with different minor allele
427 frequencies, different LD structure and different effects for causal variants. Wientjes
428 et al. (2016)[22] explicitly addressed the problem of different effects for causal
429 variants (i.e. genetic correlation less than one) when combining data from two
430 populations. Individuals from different populations share genomic relationships that
431 are lower than those among members within each population. Evidence in literature
432 suggests low prediction accuracies when using information from different breeds or
433 populations, which could be viewed as predicting from populations with very large
434 N_e. Moreover, we have not considered historical population dynamics such as
435 bottleneck and admixture, but assumed a constant N_e over the historical generations,
436 which leads to simplifications that make the formulae tractable and easy to derive.
437 Further work is required to extend the theory accounting for admixture populations
438 and historical population dynamics.
439

440 We have shown an improved theory for the prediction of the effective number of
441 chromosome segments, which is a key parameter in genomic prediction accuracy[7].
442 The theory accounts for the correlation between relationships at different
443 chromosomes and as a result the effective number of chromosome segments is
444 smaller than predicted from previous theory[5, 6, 21]. As a result, the increase of the
445 genomic prediction accuracy appears to be less reliant on higher marker density
446 unless N_e is very large (e.g. > 10,000) (Figure 2), compared to what have been
447 quantified by previous theory[5, 6, 21]. The previous theory overestimates M_e (mostly
448 due to neglecting correlation between chromosomes), therefore underestimates the
449 proportion of genetic variance at QTL captured by markers. Little improvement of
450 prediction accuracy with increasing SNP marker density has been empirically
451 observed in a number of studies[39-41]. This may also have important implication in
452 genomic prediction as to designing marker density in animal, plant and human
453 genetics.
454
455 The ability to quantify the accuracy in relation to various degrees of relationships (e.g.
456 close relatives, distant relatives, local or extensive population sample) is important for
457 predicting outcomes of genomic prediction for specific designs. This study has
458 addressed this question, and the theory has been implemented in MTG2 software
459 (https://sites.google.com/site/honglee0707/mtg2). Therefore, a user can know the
460 expected prediction accuracy and the power[26] before designing an experiment of
461 genomic prediction. Our approach can be applied both before and after collecting the
462 data.
463
464

ACKNOWLEDGEMENTS

This research is supported by the Australian National Health and Medical Research Council (APP1080157), the Australian Research Council (DP160102126, FT160100229) and the Australian Sheep Industry Cooperative Research Centre. The Framingham Heart Study is conducted and supported by the National Heart, Lung, and Blood Institute (NHLBI) in collaboration with Boston University (Contract No. N01-HC-25195). This manuscript was not prepared in collaboration with investigators of the Framingham Heart Study and does not necessarily reflect the opinions or views of the Framingham Heart Study, Boston University, or NHLBI. Funding for SHARe Affymetrix genotyping was provided by NHLBI Contract N02-HL-64278. SHARe Illumina genotyping was provided under an agreement between Illumina and Boston University. The authors acknowledge useful discussion with Han Mulder that contributed to a clearer paper.

DISCLOSURE DECLARATION

The authors declare no competing financial interests.

Table 1. The sample size (N) and empirically observed M_e in each of three different reference data sets and combined data set in the Framingham data analysis.

	N_i (standard deviation)	M_e (standard deviation)
Reference #1	N_1 = 617 (19)	2254 (50)
Reference #2	N_2 = 1254 (30)	3989 (104)
Reference #3	N_3 = 1572 (33)	28848 (920)
Combined all	N_{all} = 3443 (0)	4836 (106)

The values were averaged over 100 replicates.

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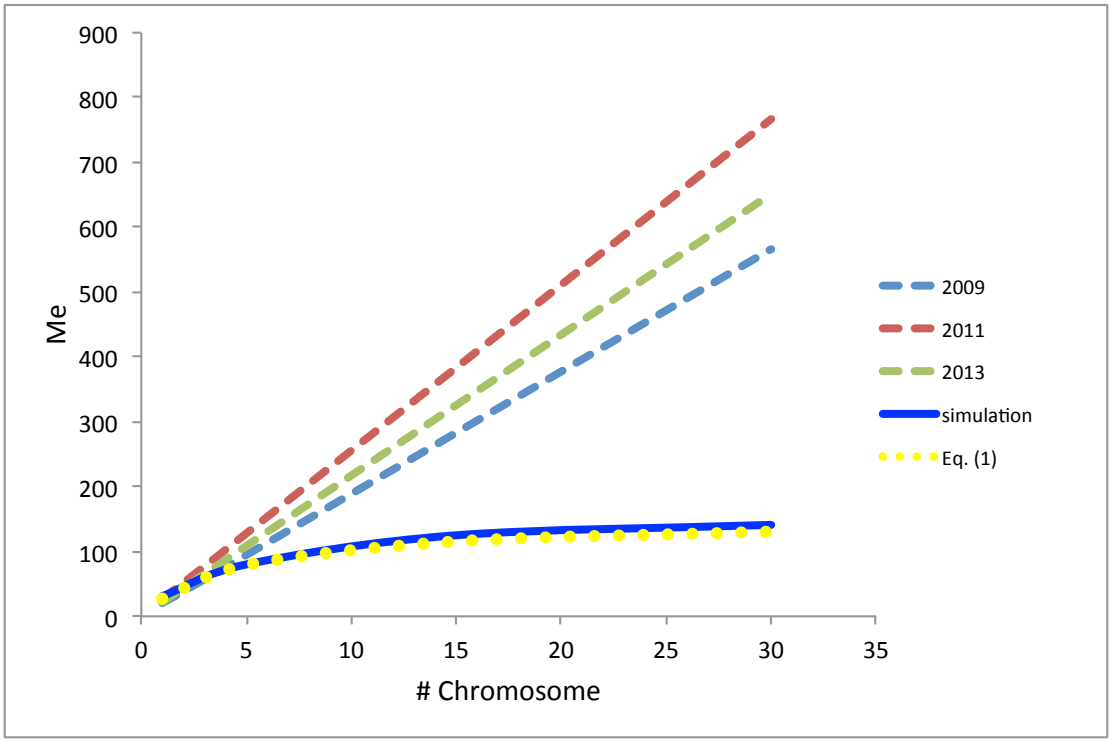
A.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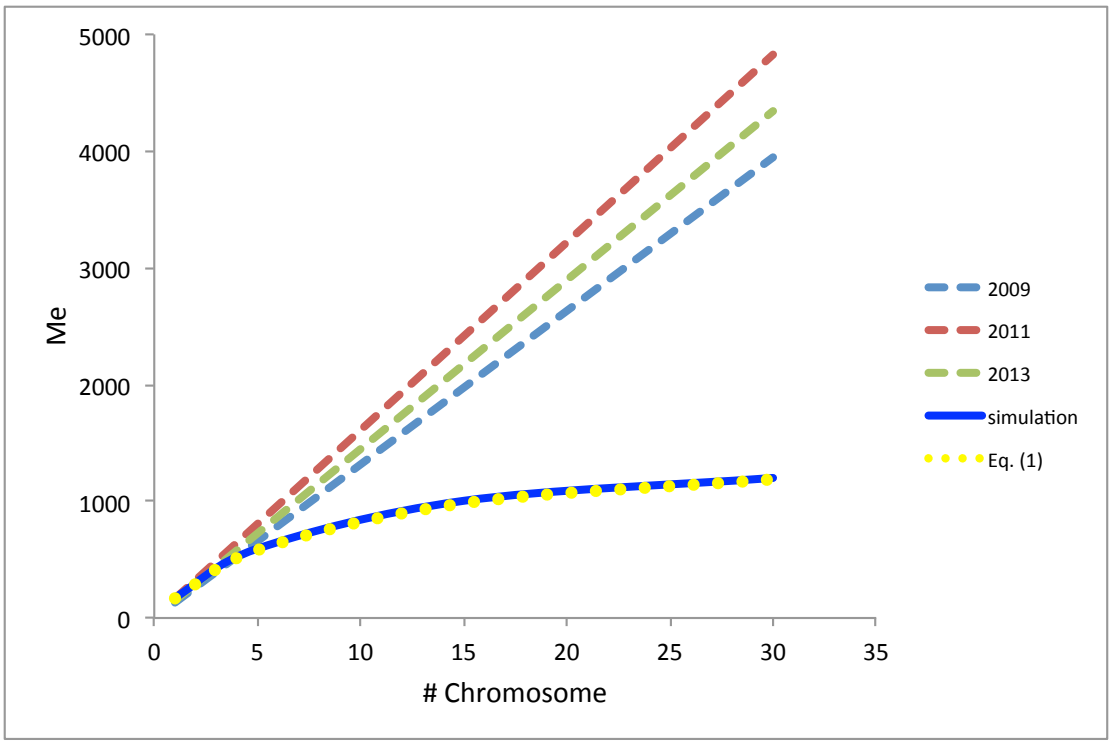
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C.

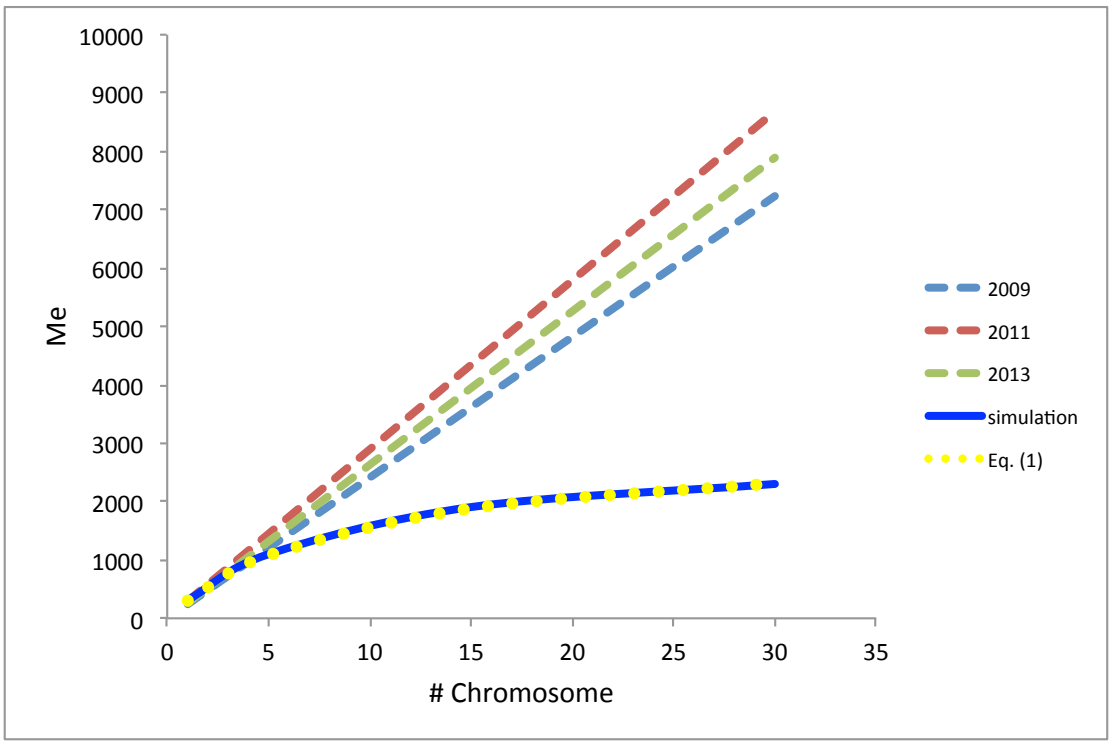
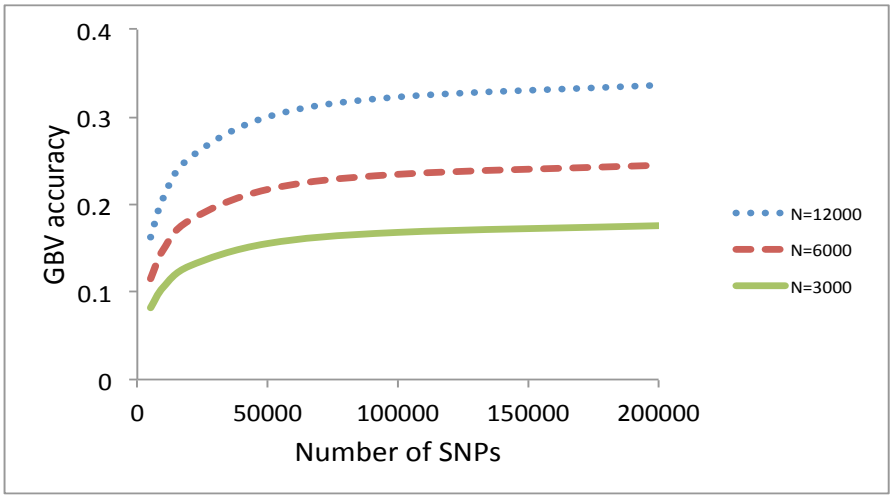


Figure 1. Expected effective number of chromosome segments (M_e) from previous studies in 2009[6], 2011[5] and 2013[21] and from Eq. (1) in this study, compared to empirically observed from M_e simulation when varying the number of chromosomes each with 1 Morgan long. Effective population size was used as N_e =50 **(A)**, 500 **(B)** and 1000 **(C)**. This confirms the result from Lee et al. (2017)[7].

A.



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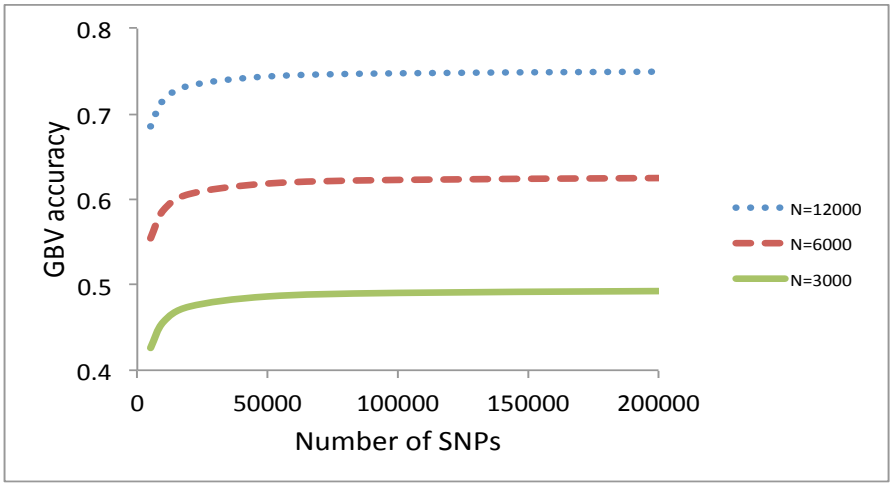

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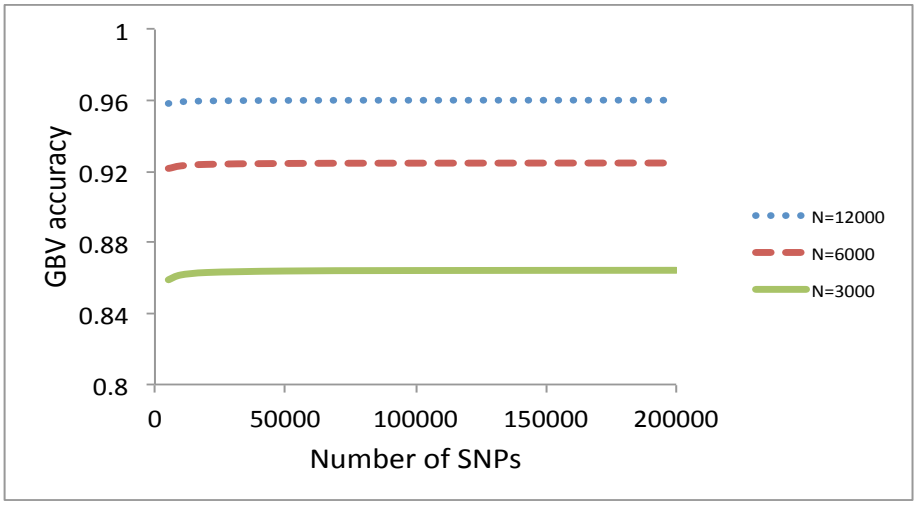

Figure 2. Accuracy of GBV when varying the number of SNPs for N_e = 10,000 **(A)**, 1000 **(B)** and 100 **(C)**. The sample size in the reference data was N=12,000, 6000 or 3000. The heritability was 0.25.

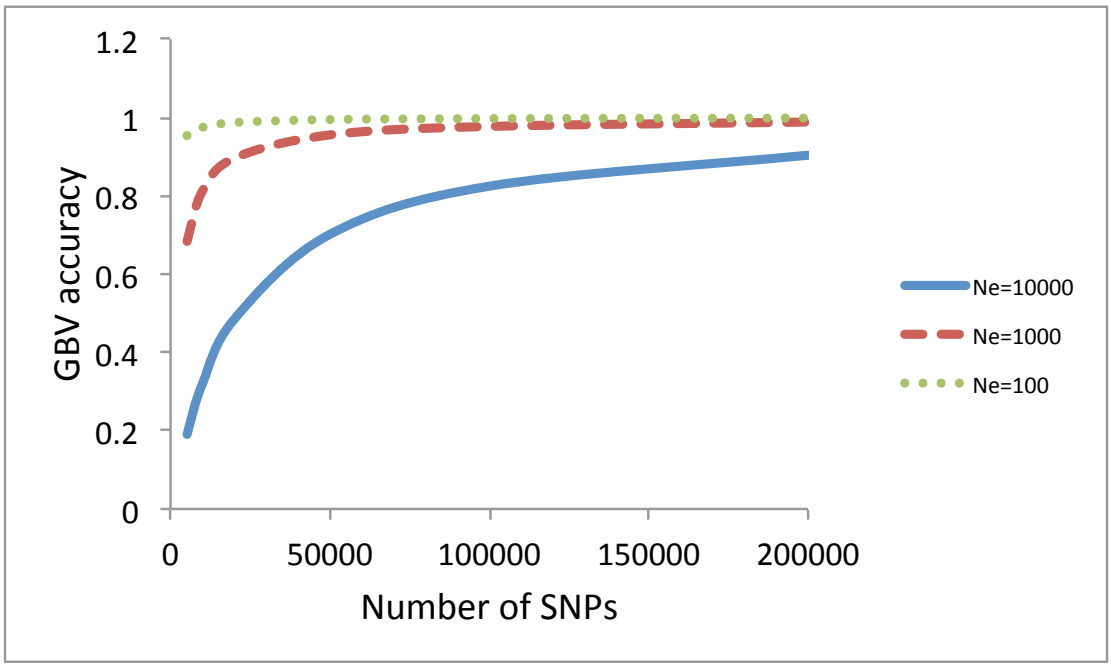

Figure 3. The proportion of genetic variance at QTL captured by markers (b = M / (M_e + M) when varying the number of SNPs for N_e = 10,000, 1000 and 100.

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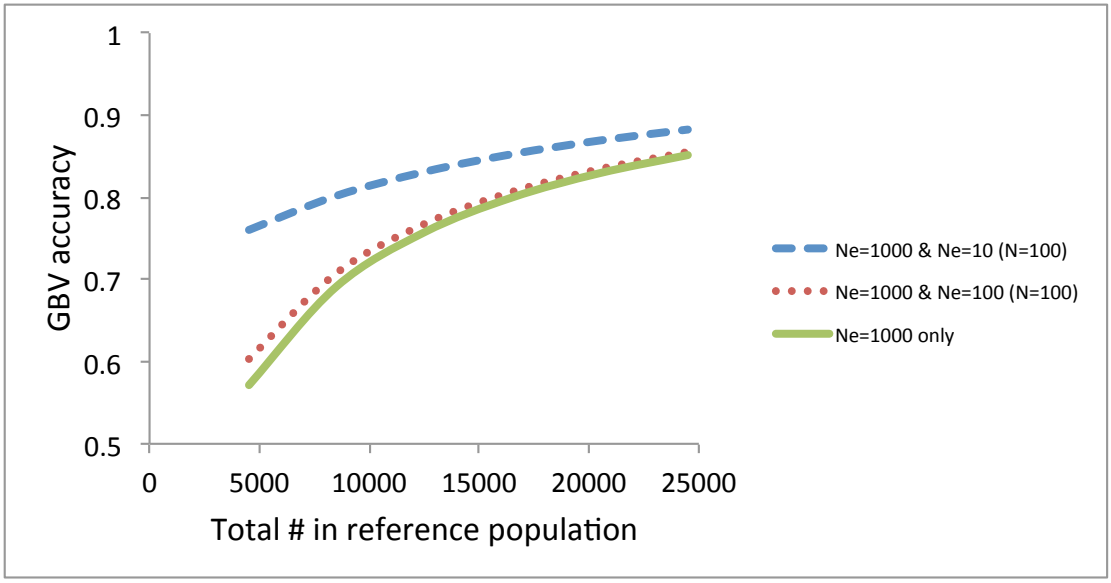
678 A.



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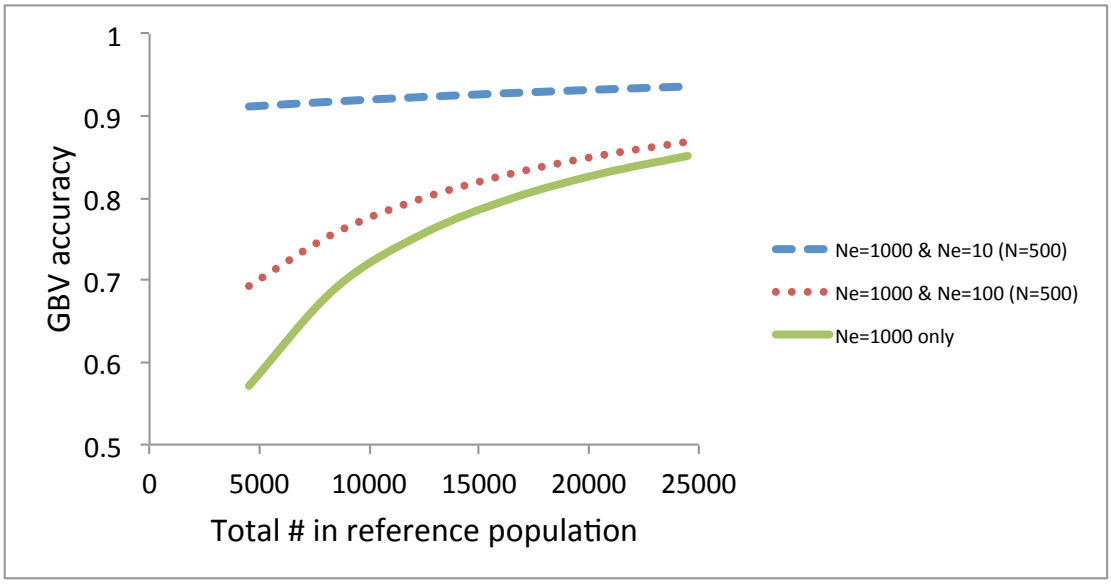
681 B.



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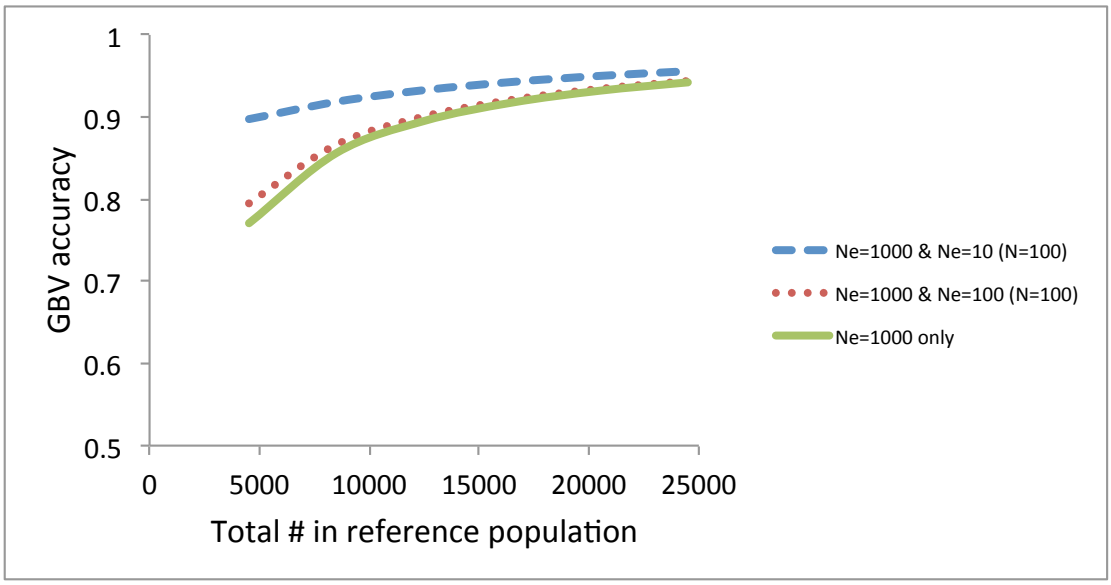
683
684 Figure 4. Accuracy of GBV when adding 100 individuals (N=100) **(A)** or 500
685 individuals (N=500) **(B)** of N_e=100 or N_e=10 to the reference population of N_e=1000.
686 The heritability was 0.25.
687
688

A.



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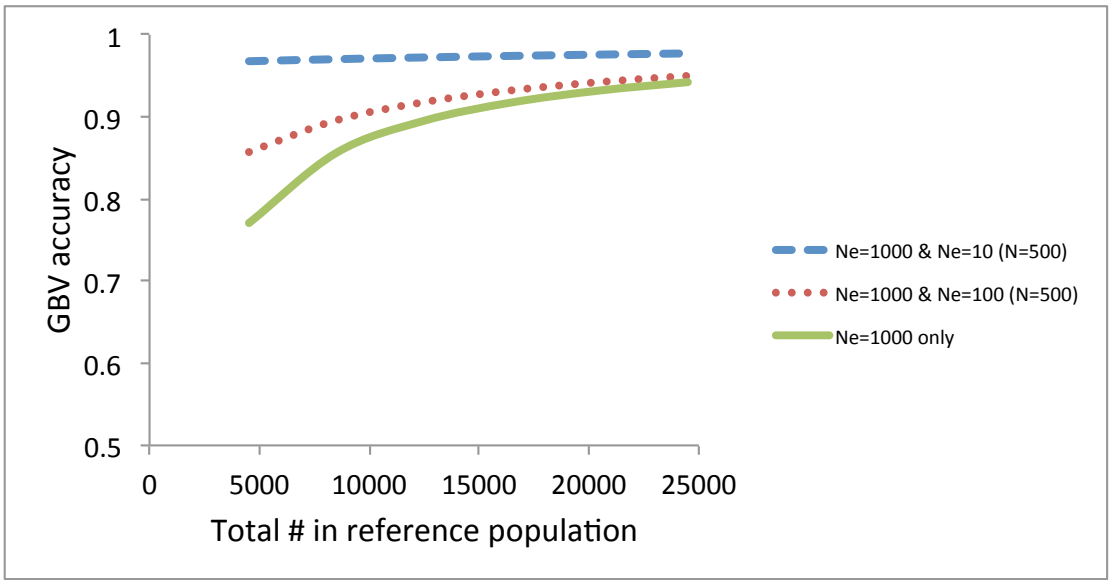

Figure 5. Accuracy of GBV when adding 100 individuals (N=100) **(A)** or 500 individuals (N=500) **(B)** of N_e=100 or N_e=10 to the reference population of N_e=1000. The heritability was 0.25. The heritability was 0.75.

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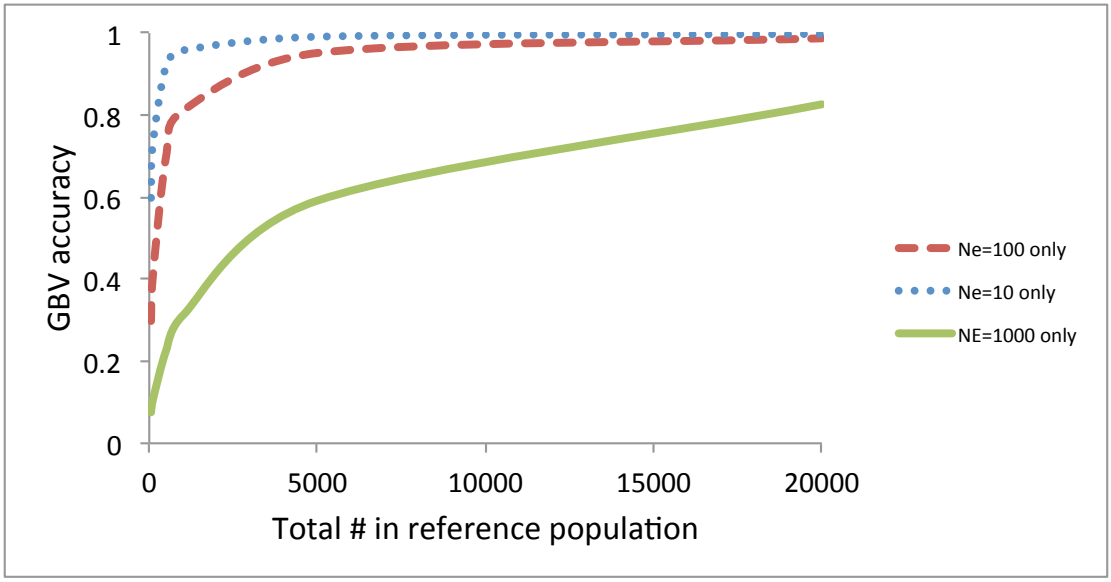

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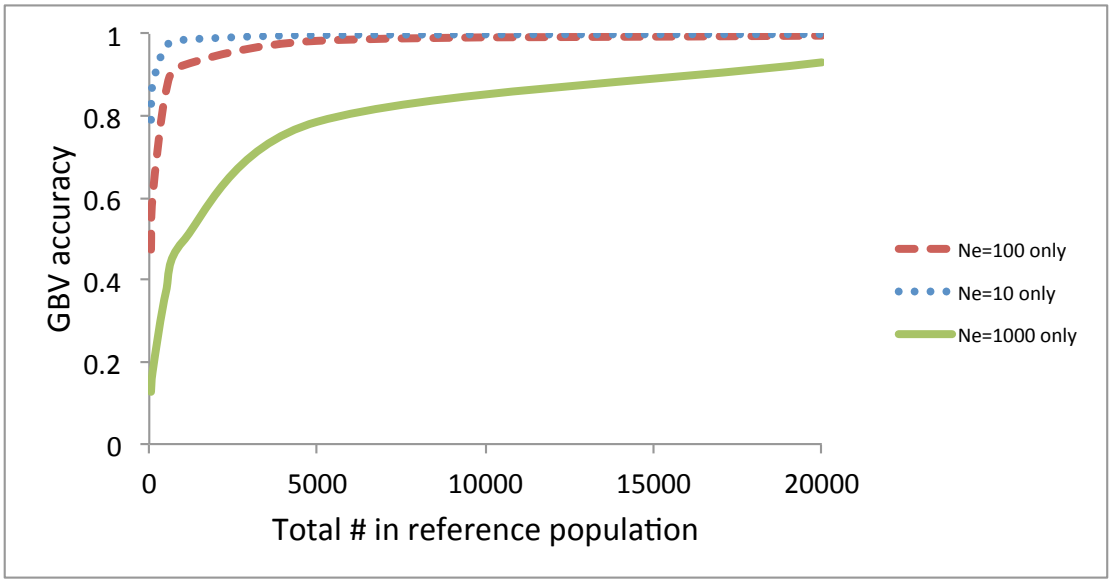
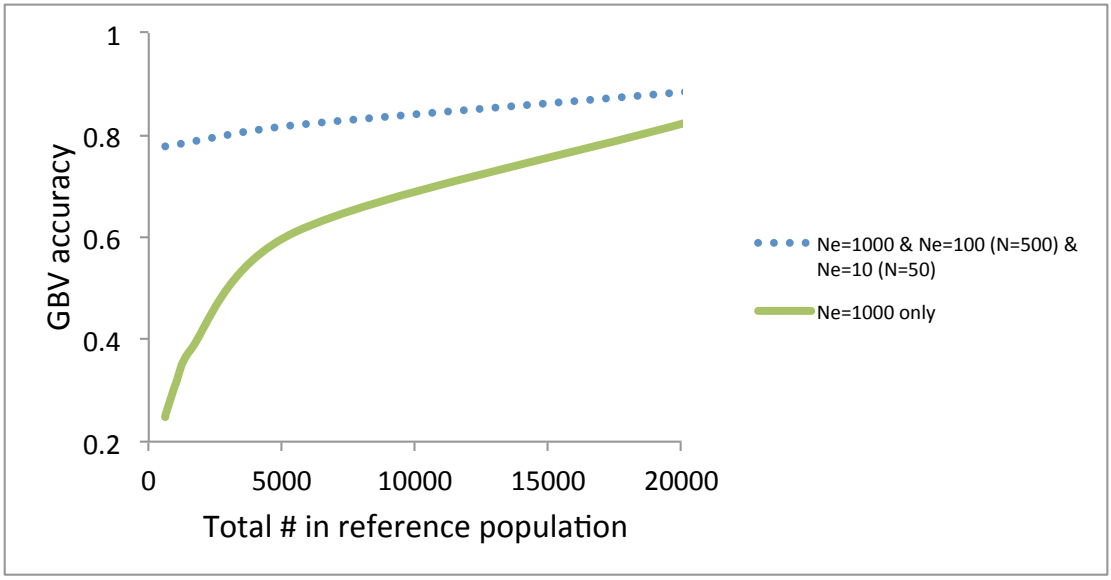


Figure 6. Accuracy of GBV when using N_e=1000 only, N_e=100 only and N_e=10 only with a heritability of 0.25 **(A),** and with a heritability of 0.75 **(B).**
For N_e=10 only, the accuracy at a sample size of 100 was 0.73 **(A)** and 0.88 **(B).** For N_e=100 only, the accuracy at a sample size of 1000 was 0.81 **(A)** and 0.92 **(B).** For N_e=1000 only, the accuracy at a sample size of 20,000 was 0.83 **(A)** and 0.93 **(B).**

A.



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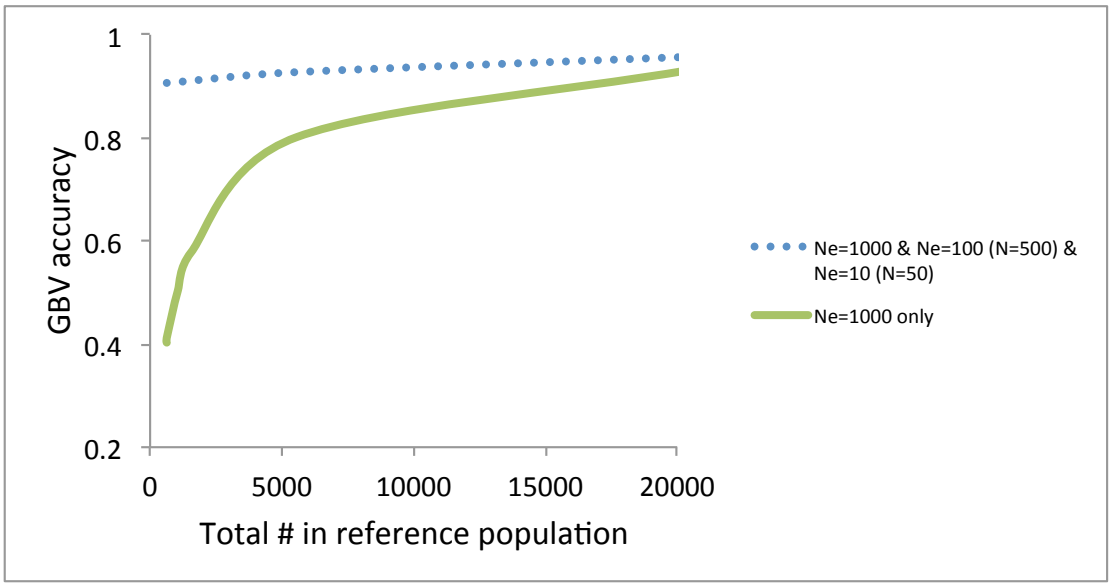

Figure 7. Accuracy of GBV when using a composite design, e.g. N_e=1000 + N_e=100 (N=500) + N_e=10 (N=50), compared to Ne=1000 only with a heritability of 0.25 **(A)** and with a heritability of 0.75 **(B).**

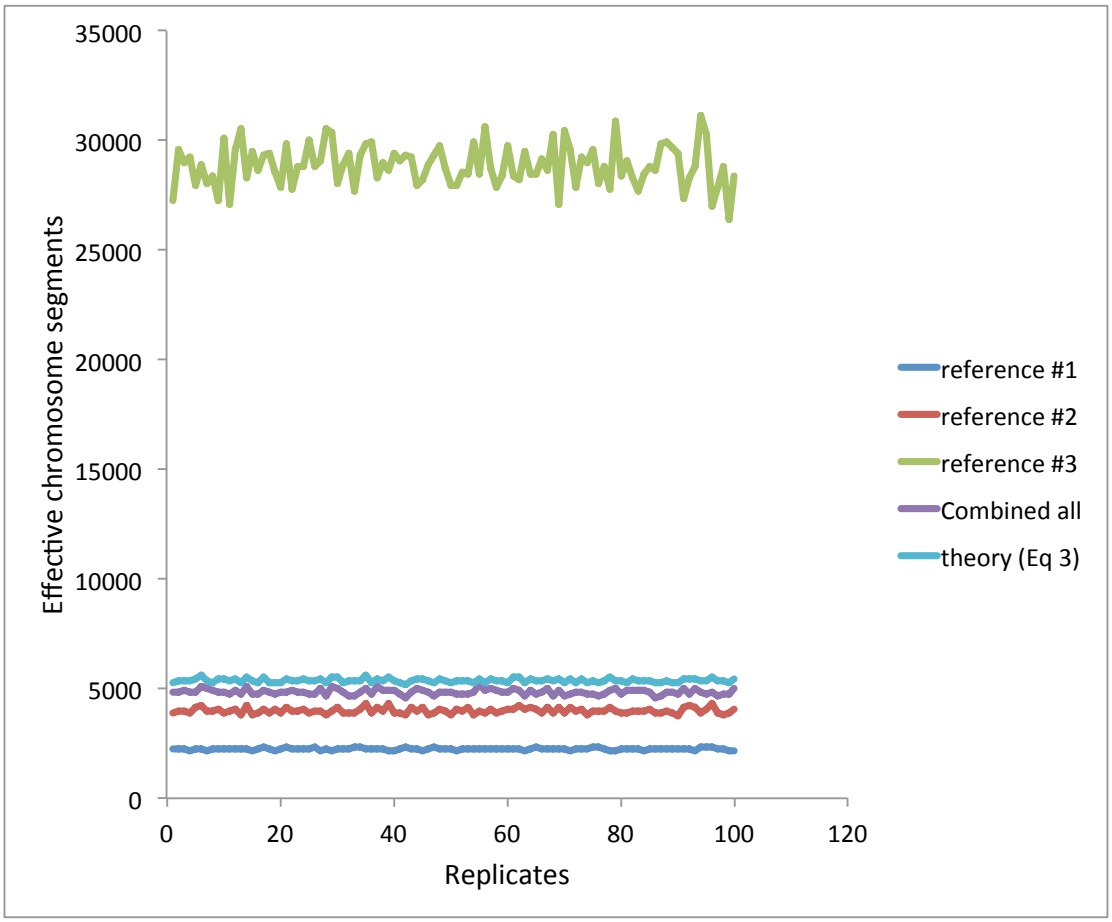

Figure 8. When using Framingham data, empirically estimated M_e based on each of the reference data sets and combined data. Empirically estimated M_e based on combined data is approximately agreed with that from theory (Eq. 5).

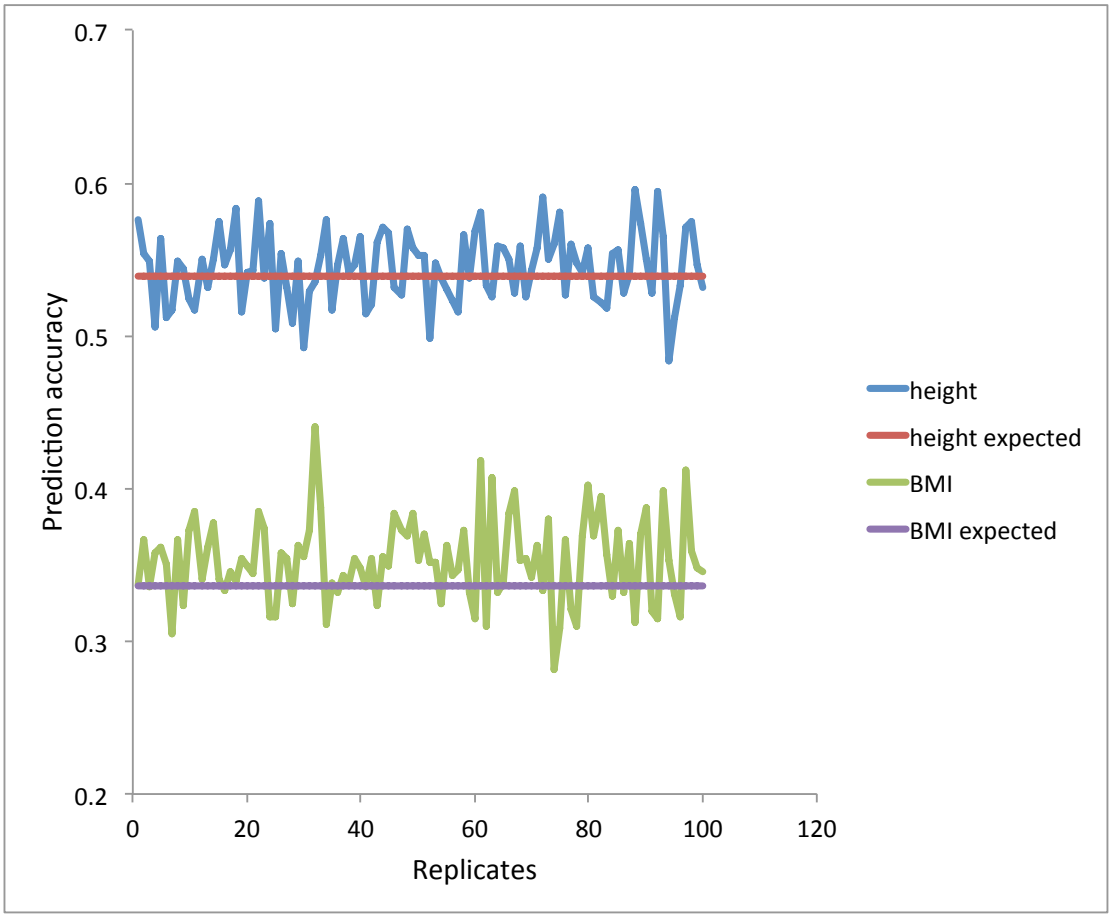

Figure 9. When using Framingham data, observed prediction accuracy and expected prediction accuracy with given M_e and N (from Eq. (3)) are agreed well. The reported heritability, h^2=0.8 [33-35] for height and h^2=0.46[36, 37] for BMI, were used.

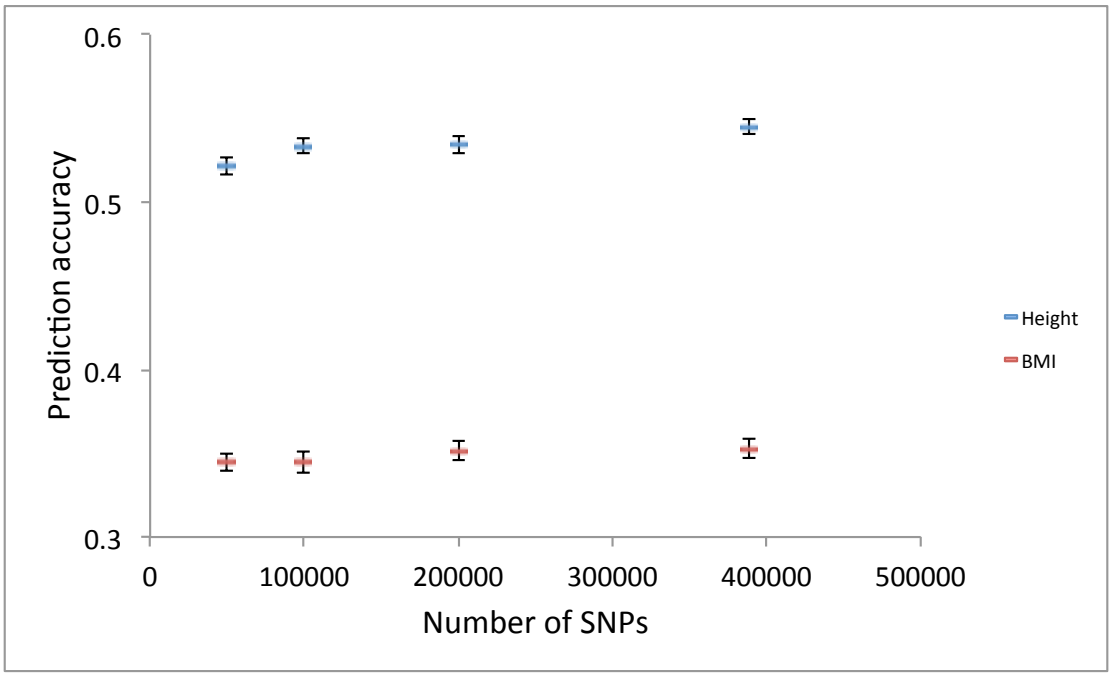

Figure 10. When using Framingham data, the prediction accuracy is not much decreased even with 50,000 SNPs that were randomly selected from 389,265 SNPs.