Abstract
A major transition in human population structure is currently under way, moving from a historical metapopulation, comprising small and mainly rural endogamous communities, to large and increasingly panmictic urban populations. This process is predicted to increase outbreeding, and preliminary data from genomic surveys have helped to quantify the potential magnitude of the effects. Population genetic trends of this nature should result in a reduced burden of recessive disorders, and have a favourable impact on complex diseases influenced by partially recessive genetic variants of smaller effect. The overall outcome is expected to be beneficial for a range of traits associated with human health and disease that show dominance variance.

Introduction
The demographic structure of human populations has changed dramatically over the last 200 years, resulting in major changes in the size and composition of gene pools. Prior to the 19th century, a large majority of the world’s population lived and reproduced in small communities with restricted mate choice. During the last two centuries, the total human population has expanded from 1 to over 6.2 billion, and the percentage of the global population living in major towns and cities has increased from 2% to nearly 50% [1]. The migration of people from small, often isolated and genetically quite uniform communities to larger conurbations has led to a decline in endogamous and consanguineous marriage and to increased rates of marriage between partners from different geographical, ethnic, religious and social backgrounds [2,3]. Over the last 50 years, the process of ‘isolate break-up’ has led to the admixture of many genetically differentiated populations. This has increasingly involved intercontinental migration which, in conjunction with rapid urbanization, has further contributed to gene flow and resulted in more diverse breeding pools. Mutation has also increased genetic diversity through the generation of large numbers of new rare variants [4,5]. Collectively, the changes have led to a decrease in the level of population substructure and linkage disequilibrium (LD) in European populations [6,7].

Empirical evidence of changing genetic structure
Demographic data
Consanguineous marriage continues to be popular in many parts of Asia and Africa [8], although in East Asia a marked general decline in consanguinity has occurred since the mid-20th century. Elsewhere, the picture is mixed with, for example, a partial reduction in consanguinity in South India, but no apparent change in the approximately 50% of marriages contracted between first cousins in Pakistan. In the Middle East, a decline in consanguinity is seen in some Arab countries but there has been an increase in others [2]. In Iran, marked inter-ethnic differences in the prevalence of consanguinity make any national trend difficult to determine [9]. Cousin marriage has recently become a much more important issue in Europe, with over 10 million migrants from regions with high levels of consanguinity (North Africa, the Middle East, Turkey, Central Asia, and South Asia) now resident across the continent. Equivalent information on the level of consanguinity among migrant communities in the USA is hampered by the fact that first cousin marriage is prohibited or a criminal offence in 31 of the 50 states [2].

Genetic data
A predicted effect of the admixture of individuals from different genetic populations is an increase in average individual genome-wide heterozygosity, $h$, as previously reported for morphometric and biochemical parameters among younger Israelis [10]. Using genomic data, Rudan and colleagues [11] measured $h$ in Croatian populations and demonstrated that levels are increasing through urbanization, isolate break-up and admixture. The observed wide range of variation in $h$ was unlikely to be stochastic since it was closely correlated with individual genetic histories, leading to the conclusion that population

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**BP**, blood pressure; **kb**, kilobases; **LD**, linkage disequilibrium; **ROH**, short runs of homozygosity; **SNP**, single nucleotide polymorphism.
substructure, recent inbreeding and population admixture were the underlying mechanisms.

High-density single nucleotide polymorphism (SNP) analysis has been used to monitor the impact of these population changes on individual and community levels of autozygosity - defined as homozygosity in which each allele is derived from the same ancestral gene (that is, is identical by descent). Whole-genome SNP data have demonstrated short runs of homozygosity (ROH) measuring tens of kilobases (kb) and covering up to one-third of the autosomal genome, which are indicative of ancient LD patterns [12]. Longer ROH tracts (for example, >500 kb) provide a useful measure of more recent consanguinity. These regions can be used to infer the autozygosity status of genomic regions and, by summing the overall length of ROH regions above a minimum size, they provide a good summary measure of individual genome-wide homozygosity [12]. Long genomic segments containing ROH, which reflect inheritance from a recent common ancestor, are common in many populations, including Han Chinese, indigenous Taiwanese, Caucasians and African Americans [13-19]. Increased urbanization and population admixture in the USA have been associated with a steady decrease in the size and frequency of ROH regions over the course of the 20th century: there has been an estimated 14% decrease in ROH frequency, a 24% decrease in the amount of the genome in ROH, and a 30% reduction in the inbreeding coefficient, $F_{ID}$ [20]. Since Europeans have the smallest among-population variance component, the trend of decreasing autozygosity with younger chronological age in the North American population of European ancestry studied by Nalls et al. [20] has important implications for the populations of other continents, where urbanization may exert even larger effects on genomic organization.

**Predicted health effects**

**Impact on the prevalence of recessive single-gene disorders**

A reduction in autozygosity through outbreeding should decrease the burden of recessive monogenic disorders in communities with a high prevalence of consanguineous marriages [21-23]. A detailed prospective study of the Pakistani community in Birmingham, UK, indicated a significantly higher prevalence of autosomal recessive disorders among the progeny of consanguineous couples [24]. On the basis of these data, it has been calculated that there would be an approximate 7/1,000 increase in autosomal recessive disorders per 0.01 increase in the mean coefficient of inbreeding [25]. If this estimate is applied to the reduction in inbreeding coefficient reported by Nalls et al. [20], then one could infer that approximately 1% of the annual births affected with an autosomal recessive disorder have been avoided in the North American population due to the 100-year population trends that have been identified.

Considered on a longer time scale, the reduced numbers of affected homozygotes will, however, result in decreased selection against the causative disease alleles and eventually result in their increased incidence in the gene pool. At the same time, due to isolate break-up, a higher proportion of affected individuals will be compound heterozygotes with different mutations inherited from each parent.

**Impact on the prevalence of complex diseases influenced by partially recessive genetic variants**

Outbreeding has long been known to influence complex as well as monogenic traits that are influenced by recessive or partially recessive variants [26]. How large is this effect likely to be? Recessivity is thought to be a property of multi-enzyme systems, which results in enzymatic safety margins, so that a reduction in the activity of a single allele will generally have little impact on the metabolic pathway [27]. The majority of genetic changes in enzymes, which make up 25 to 30% of gene products [28], are expected to show recessive or partially recessive phenotypes, whereas a smaller proportion is expected for non-enzymic proteins. Deleterious mutations are more likely to be recessive, while neutral or small-effect mutations are more often additive [26]. A wide variety of complex traits in many organisms are influenced by inbreeding, although it is unclear why the genetic (dominance) effects tend to be unidirectional. Most of the variants affecting human complex traits remain to be identified but a recent study suggested that partially recessive effects of relatively high penetrance may explain a proportion of the genetic predisposition to schizophrenia [16]. Therefore, just as the offspring of consanguineous matings may have lower mean health and fitness because of the homozygous expression of detrimental recessive alleles [29-32], similar effects could operate with the more numerous partially recessive variants influencing complex diseases.

**Impact on variation in quantitative traits underlying complex diseases**

In theory, any increase in individual genome-wide heterozygosity would be expected to influence variation in biological traits that show significant variance due to recessive alleles (dominance variance) [33,34], such as systolic blood pressure (BP), total cholesterol and low-density lipoprotein cholesterol [35,36]. Additionally, it has been proposed that these changes may have a significant impact in modifying the epigenetic, epistatic and polygenic pathways that influence complex traits [20].

Rudan and colleagues [29] found a positive linear relationship between the inbreeding coefficient and both systolic and diastolic BP in a Croatian population, with recessive or partially recessive genetic variants accounting for 10 to 15% of the total variation in BP. A decrease in mean inbreeding coefficient ($F_{ID}$) of 0.01 was associated with a reduction of approximately 3 mmHg in systolic BP and 2 mmHg in diastolic BP in both sexes [29]. Applying
these findings to the change in mean inbreeding coefficient reported for the USA during the 20th century [20] would equate to an equivalent decrease of approximately 3 mmHg in systolic BP and approximately 2 mmHg in diastolic BP in both sexes.

The associations between systolic and diastolic blood pressure and coronary heart disease events and stroke have been described in a meta-analysis of 61 cohort (prospective observational) studies [37] and in the largest reported meta-analysis of randomized trials of blood pressure reduction [38]. The results indicated that cardiovascular mortality showed a constant proportional change in risk for a specified change in blood pressure (down to a diastolic BP of 70 mmHg). Regression coefficients were estimated from these data, facilitating the prediction of the proportional reduction in disease events for any age and blood pressure difference. The calculated regressions suggested that a decrease in adult diastolic and systolic BP of the magnitude derived from Rudan et al. [29] and Nalls et al. [20] would result in reductions in the incidence of coronary heart disease (and heart failure events) and stroke of approximately 5 to 10% and 10 to 15%, respectively [38].

Conclusions
The preliminary data suggesting the beneficial effects of decreased consanguinity on complex diseases [29,32,39] require replication in other populations before their general significance can be properly assessed. However, as traits that show dominance variance were responsible for some 20% of the total burden of disease in industrialized countries in 2000 (that is, hypertension 11%; hypercholesterolemia 8%) [40], even small effects on the prevalence of the common traits and conditions would have important public health implications at community and population levels. Future studies could also profitably consider other traits that showed marked secular trends during the 20th century, such as IQ, which may also have been influenced by the population genetic trends that accompany isolate break-up [41]. It is improbable that the favorable secular trends in health and life expectancy in human populations worldwide during recent decades can solely be explained by socioeconomic factors and improved health care, yet to date the influence of marriage patterns on population genetic structure has been substantially under-investigated. Until this issue is better understood, the potential role of outbreeding in the inheritance of polygenic traits and complex human diseases cannot readily be dismissed and merits further detailed study.

In purely practical terms, the predicted increase in the proportion of compound heterozygotes that will accompany outbreeding will make screening programs for recessive single-gene disorders and conditions involving partially recessive variants less predictable. However, the current rapid advances in whole-genome screening should solve this issue in a cost-effective manner.

Competing interests
The authors declare that they have no competing interests.

Authors’ contributions
All authors contributed to the text of this commentary and reviewed the final version before publication.

Acknowledgements
AHB was supported by NSF grant number 0527751.

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Published: 28 September 2009
doi:10.1186/gm91
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