Twin Research and Human Genetics

Supplementary Materials

Septic Shock: A Genome-Wide Association Study and Genetic Risk Score Analysis

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Supplementary Methods S1. ADRENAL Recruitment

Recruitment into the ADRENAL trial has been previously described (Venkatesh et al., 2018). In summary, adult septic shock patients from 69 intensive care units (ICUs) across Australia, the United Kingdom, New Zealand, Saudi Arabia, and Denmark (n = 3800) receiving mechanical ventilation were recruited from 2013 to 2017 into the double-blind, randomised, controlled trial (RCT) designed to examine the efficacy of hydrocortisone on septic shock. Patients were assigned to receive either 200 mg/day of intravenous hydrocortisone (n = 1832) or a placebo (n = 1826) for seven days or until death/discharge from the ICU (Venkatesh et al., 2018).

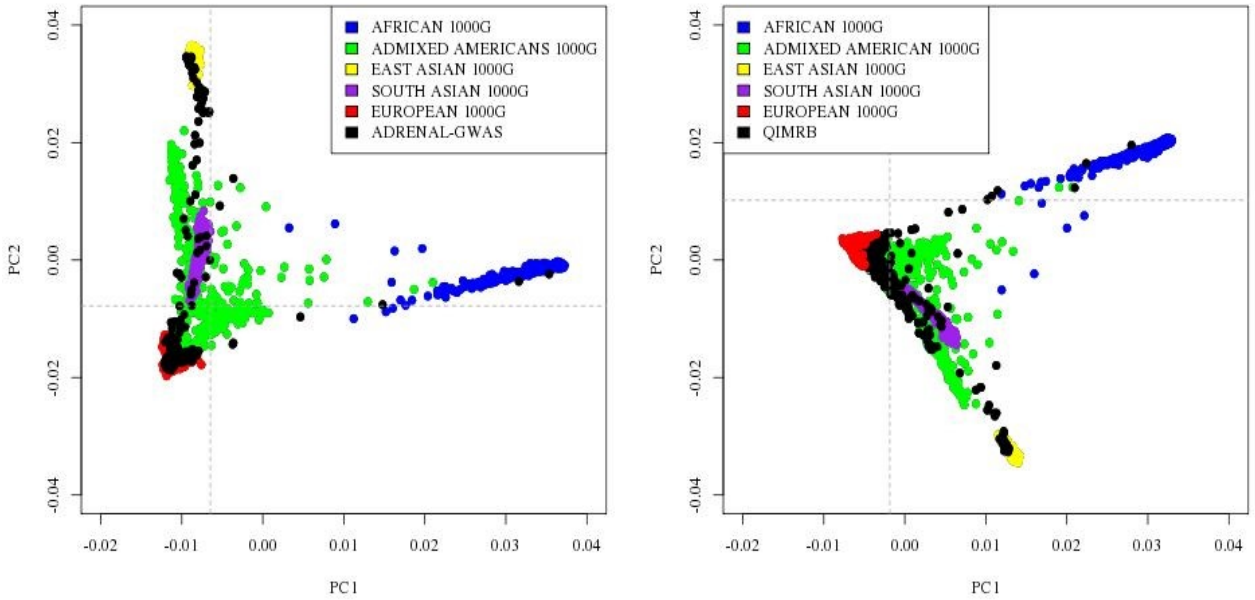
Supplementary Methods S2. ADRENAL-GWAS Outcomes

The primary outcome in both this study (ADRENAL-GWAS) and ADRENAL is death from any cause at 90-days after randomisation.

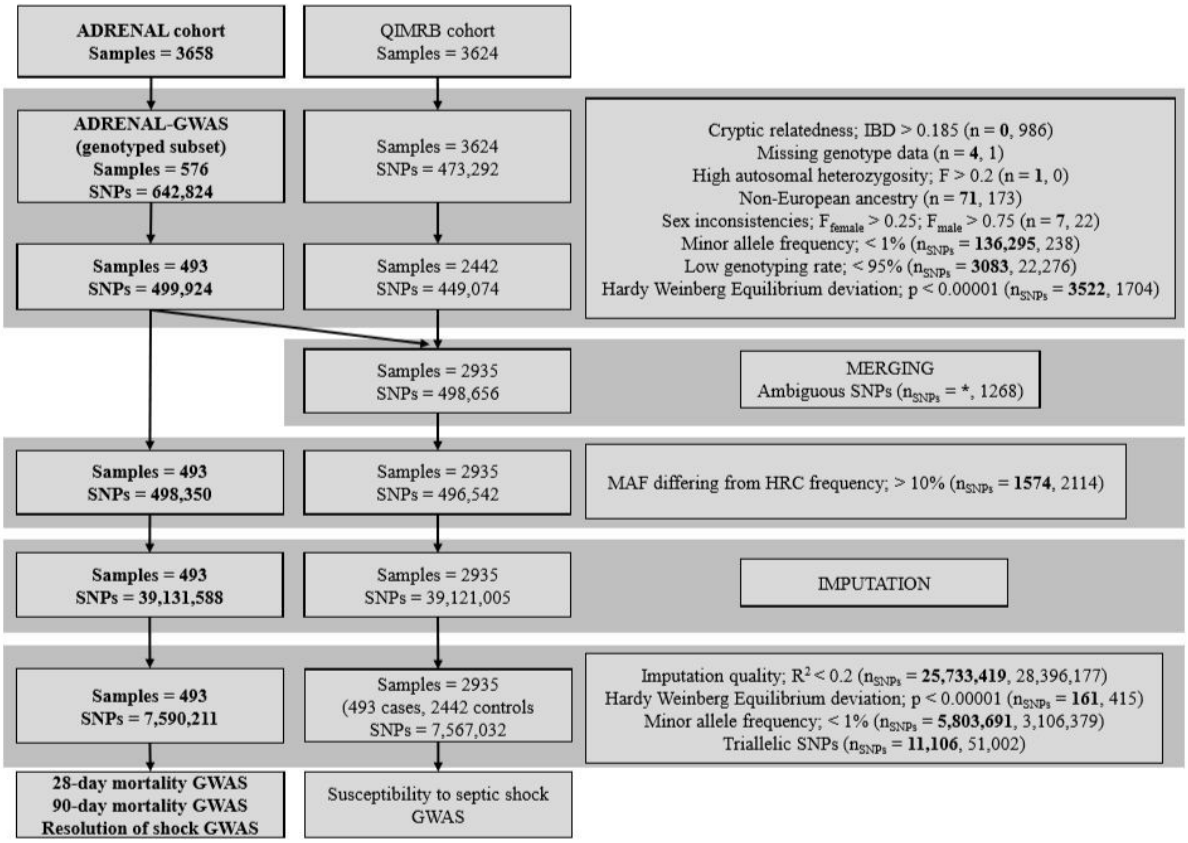
There were three secondary outcomes that were investigated in this GWAS. Firstly, death from any cause at 28-days post randomisation, which was investigated to allow comparison of results with past GWAS of sepsis. The second secondary outcome is shock resolution, which was defined as no longer requiring inotropes/vasopressors for a 24-hour period. The final secondary outcome was susceptibility to shock, which was assessed by comparing septic shock patients with unselected controls. As such, they are likely to be a random sample with respect to risk of sepsis but drawn from the same population as patient samples.

Supplementary Methods S3. Quality Control Breakdown

Pre-imputation quality control (QC) was performed on both the ADRENAL-GWAS and QIMRB datasets separately implemented using the PLINK V1.90b3.31 Software Package (Chang et al., 2015). This involved excluding one of each pair of cryptically related individuals (genome-wide proportion of alleles identical by descent; IBD > 0.185), high autosomal heterozygosity (F > 0.2), sex inconsistencies, low minor allele frequency (MAF < 1%), low genotyping rate (< 95%), and departure from Hardy Weinberg equilibrium ($p < 10^{-6}$). Principal components (PCs) analyses were performed on the genetic data, seeded with a subset of 2504 individuals with known ancestry from the 1000 Genomes Project (The 1000 Genomes Project Consortium et al., 2015). Individuals were excluded due to non-European ancestry (> 6 standard deviations from the 1000 Genomes European population's first and second PC centroid). The ADRENAL-GWAS cohort was then imputed against the HRCr1.1 panel using the Michigan Imputation Server that implements Eagle v2 for phasing and IMPUTE2 for imputation (Das et al., 2016; McCarthy et al., 2016). The ADRENAL-GWAS and QIMRB cohorts were merged prior to imputation for the case-control analyses, however the ADRENAL-GWAS dataset was also imputed separately, for the analyses not requiring controls. Post-imputation QC was also performed using the same thresholds as above. Additionally, SNPs with low imputation quality ($R^2 < 0.2$), ambiguous SNPs that may result in strand mix-ups (e.g. A/T and C/G SNPs), tri-allelic SNPs, and SNPs which MAF differed by greater than 10% from HRCr1.1 allele frequencies were removed. 5 The top two PCs successfully captured patterns of genetic variation distinguishing between ancestries, as individuals from the same population clustered together (Supplementary Figure S1). The number of SNPs and samples removed at each stage of analysis is detailed in Supplementary Figure S2.



Supplementary Figure S1. Plot of Ancestry Informative Principal Component (PC) Analyses for the (A) ADRENAL Cohort and the (B) QIMRB Cohort. Black points are the ADRENAL-GWAS cohort (cases; n = 576) and the QIMRB cohort (controls; n = 3624). The analysis was seeded with 2504 Europeans and non-Europeans from the 1000 Genomes Project, and points are coloured according to population ancestry (blue = African; green = Admixed Americans, yellow = East Asian; purple = South Asian, red = European). Individuals not within six standard deviations from the 1000 Genomes European population's PC1 and PC2 centroid (grey dotted lines) were removed from further analyses (ADRENAL-GWAS = 71; QIMRB = 173).

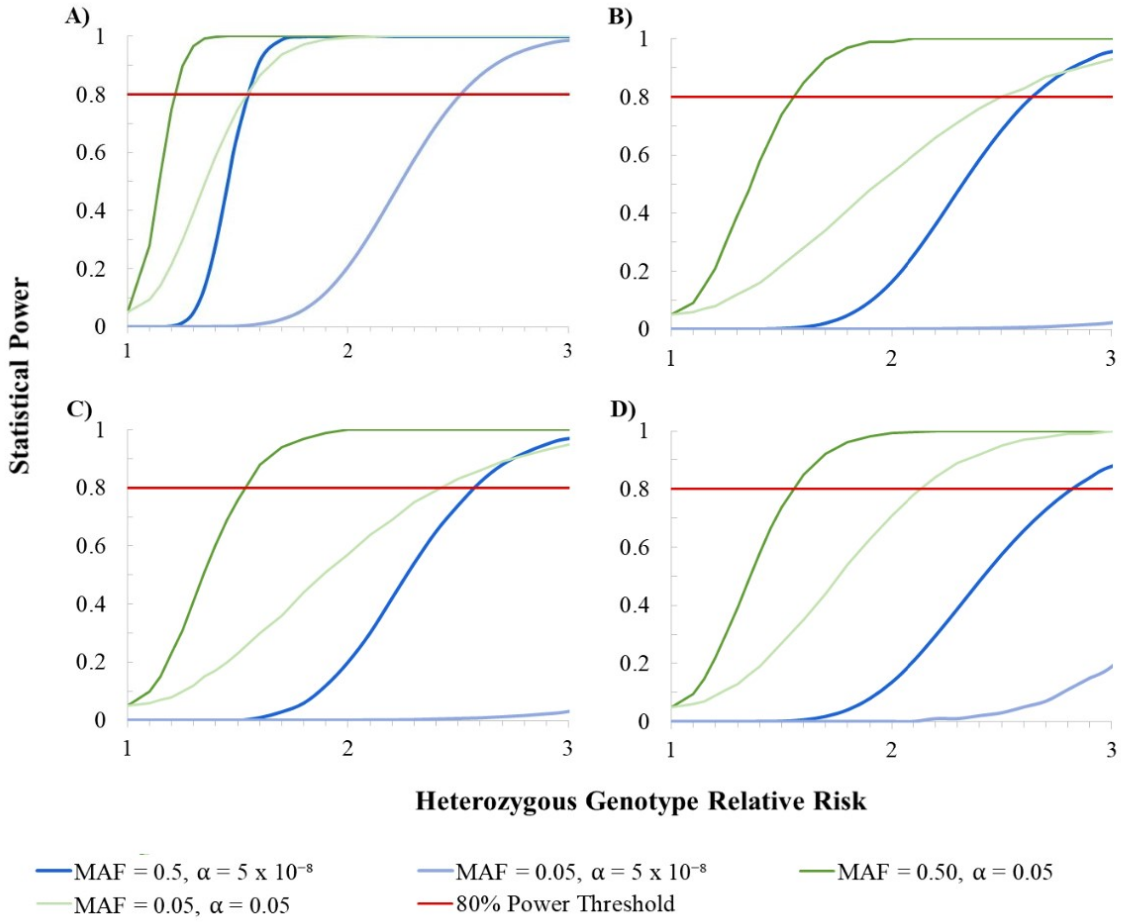


Supplementary Figure S2. Outline of Single Nucleotide Polymorphism (SNP) and Sample Quality Control (QC) Measures for the Genome-Wide Associations Studies (GWAS). Text is bolded according to the cohort which the data came from, and each box contains the number of SNPs and samples passing each step of QC. The bold text in the first column, and the bolded first number in each set of brackets refers to the ADRENAL-GWAS cohort used in the 28-day mortality GWAS. Non-bolded text in the second column, and the non-bolded second value in each set of brackets refers to the QIMRB and merged ADRENAL-GWAS-QIMRB cohort used in the septic shock GWAS. The rightmost panel contains the QC parameters and thresholds, as well as the number of variants or samples that failed the QC. Samples were filtered based upon cryptic relatedness (genome-wide proportion of alleles identical by descent; removing genotyping duplicates, twins, first-, and second-degree relatives). Samples with low call rates, and high autosomal heterozygosity deviation, non-European ancestry, low genotyping rate, and sex inconsistencies (based upon X-chromosome inbreeding coefficients) were removed. SNPs were filtered upon minor allele frequency (MAF), imputation quality, and departure from Hardy Weinberg Equilibrium (HWE). Additionally, ambiguous SNPs that may arise due to strand mix-ups (e.g. A/T and C/G SNPs), triallelic SNPs, and SNPs which MAF differed by greater than 10% from the Haplotype Reference Consortium (HRC r1.1) allele frequencies were removed. Data passing QC were used in the GWAS. * Indicates that ambiguous SNPs were not manually excluded in the ADRENAL-GWAS cohort (however IMPUTE2 did automatically address ambiguous SNPs during imputation). This extra step was only required during merging, therefore this criteria was only applied to the ADRENAL-GWAS-QIMRB merged cohort.

Methods S4. Statistical Power Calculations

The Genetic Association Study power calculator provides an estimate of the heterozygous genotype RR that the study had power to detect given the prevalence of septic shock (assuming a lifetime risk of 0.01), frequency of the risk variant (0.05 or 0.50), type I error rate (two tailed $\alpha = 5 \times 10^{-8}$ or one tailed $\alpha = 0.10$), and sample sizes (susceptibility cases = 493, controls = 2442; 28-day mortality cases = 90, controls = 403; 90-day mortality cases = 112, controls = 381; resolution of shock cases = 459, controls = 34) (Johnson & Abecasis, 2017). A multiplicative model of risk (on the odds scale) was assumed for this allelic test, and that the risk locus had been genotyped ($r^2 = 1$). As septic shock has a low prevalence in the general population, the RR approximates the odds ratio (Greenland & Thomas, 1982; Mayr et al., 2014; Waltoft et al., 2015).

The most powerful study was the susceptibility to septic shock GWAS. Here for genome-wide association analyses ($\alpha = 5 \times 10^{-8}$), we expect 80% power to detect variants with a heterozygous relative risk of 1.55 and 2.52 for a risk allele frequency of 0.50 and 0.05 respectively (Supplementary Figure S3, Supplementary Table S1). For replication of previous findings (i.e. $\alpha = 0.05$), there is 80% power to detect variants with a heterozygous RR of 1.22 and 1.54 for a risk allele frequency of 0.50 and 0.05 respectively. Our power calculations suggest that our study is adequately powered to discover common loci of relatively large effect (e.g. in the major histocompatibility region) and to confirm variants reported in previous GWAS of sepsis.

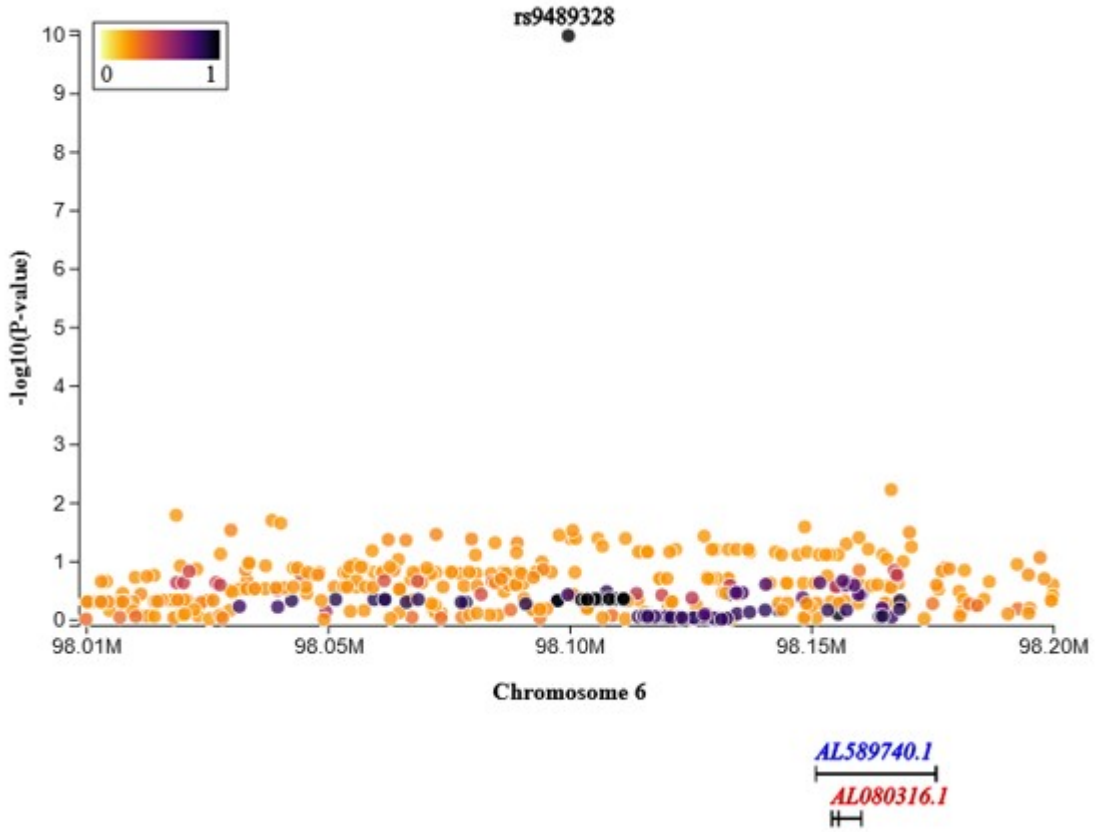


Supplementary Figure S3. Power Calculations for Genetic Tests of Association in the four ADRENAL-GWAS Studies A) Susceptibility to Septic Shock, B) 28-Day Mortality, C) 90-Day Mortality, and D) Resolution of shock. Calculations performed using the Genetic Association Study Power Calculator (Disease model = multiplicative; Prevalence = 0.01; minor allele frequency (MAF) = 0.05 and 0.50; Significance level (α) = 5 x 10^{-8}, and 0.05 for two tailed test of significance) with varying numbers of cases and controls (A) N_{Cases} = 493, $N_{Controls}$ = 2442; B) N_{Cases} = 90, $N_{Controls}$ = 403; C) N_{Cases} = 112, $N_{Controls}$ = 381; D) N_{Cases} = 459, $N_{Controls}$ = 34).

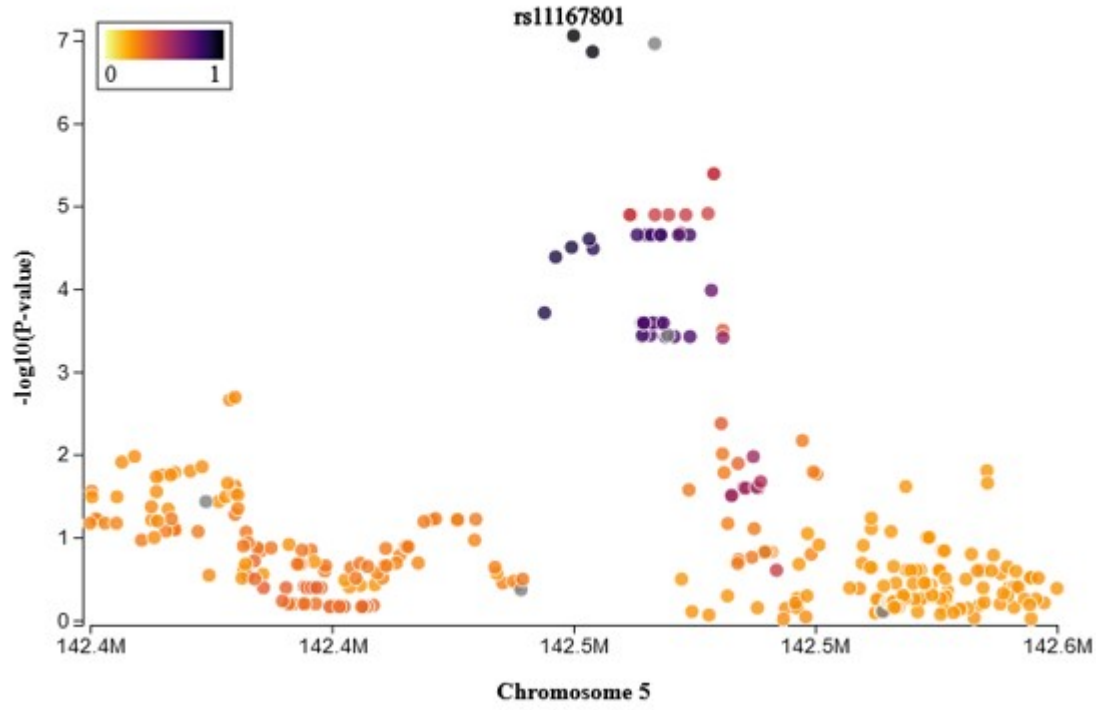
Supplementary Table S1. Results of power calculations demonstrating the relative risk (RR) that each study had 80% power to detect given the significance threshold (α) and minor allele frequency (MAF).

Parameters:	**$\alpha = 5 \times 10^{-8}$ MAF = 0.50**	**$\alpha = 5 \times 10^{-8}$ MAF = 0.05**	**α = 0·05 MAF = 0.50**	**α = 0·05 MAF = 0.05**
Study	**RR**	**RR**	**RR**	**RR**
Susceptibility:	1.55	2.52	1.22	1.54
28-Day Mortality:	2.64	6.18	1.55	2.51
90-Day Mortality:	2.57	5.82	1.53	2.42
Resolution of Shock:	2.82	3.96	1.55	2.13

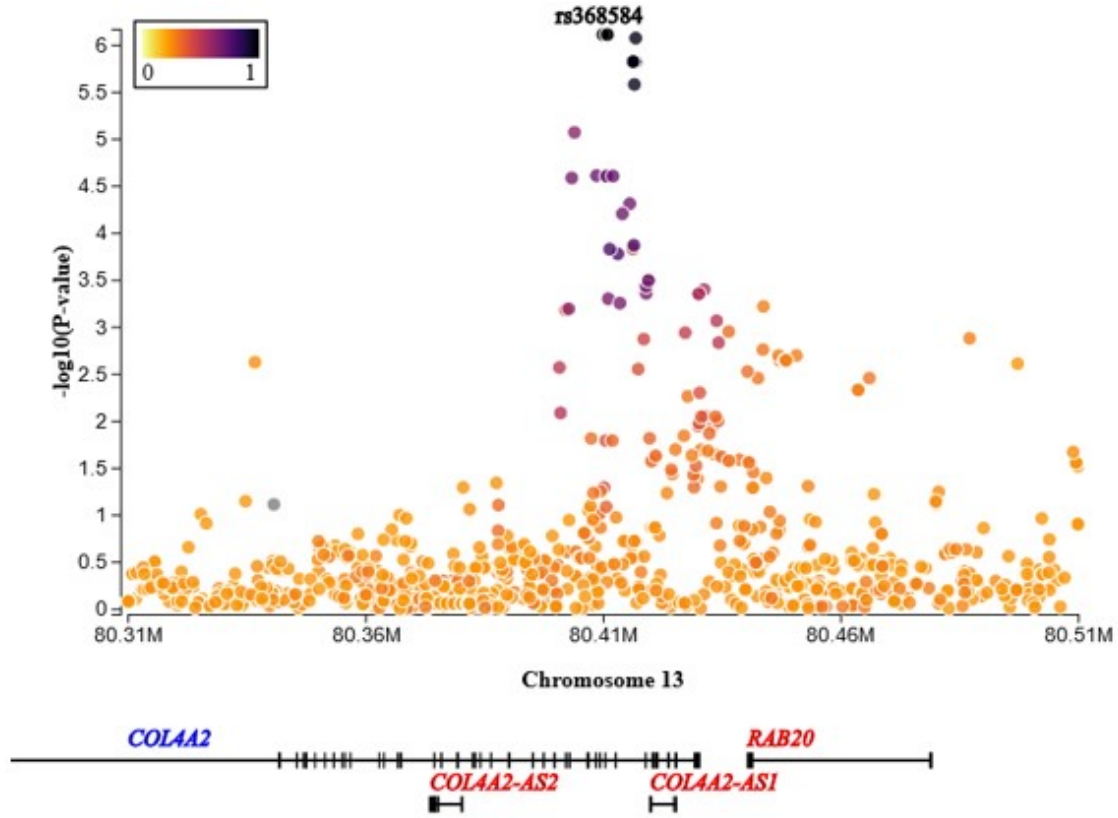
A) Regional plot for rs94893328 from the susceptibility to shock GWAS



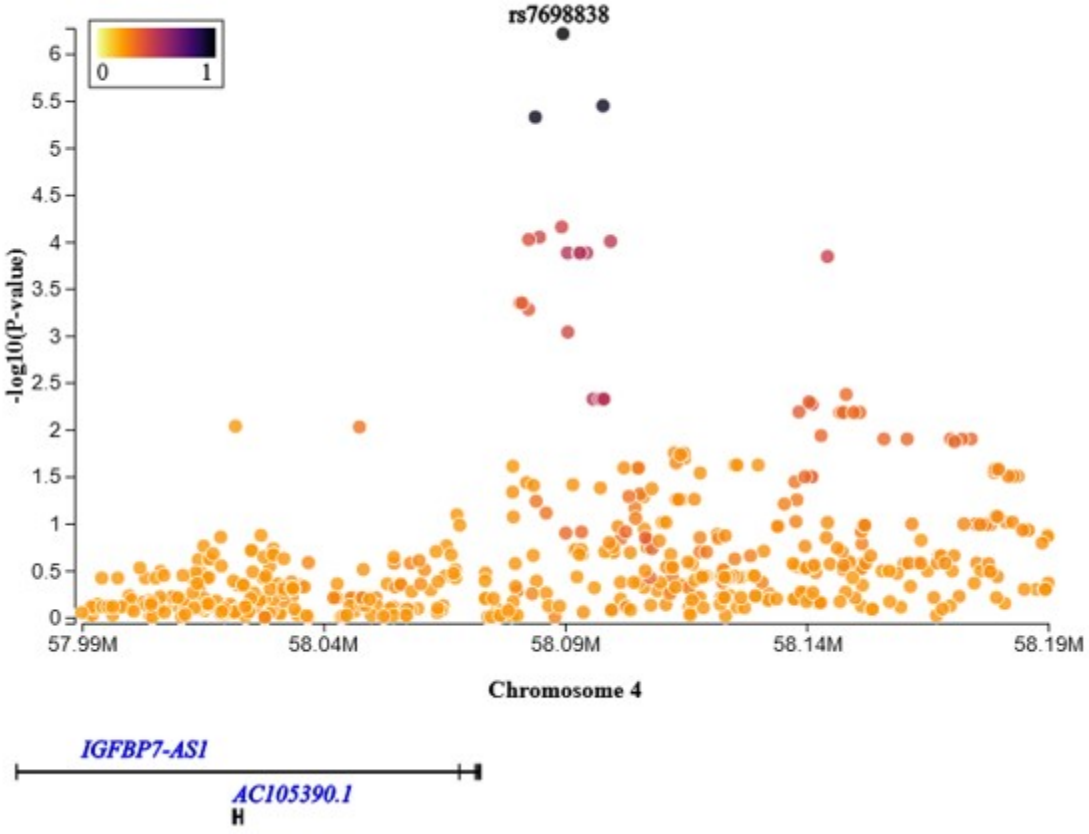
B) Regional plot for rs11167801 from the resolution of shock GWAS

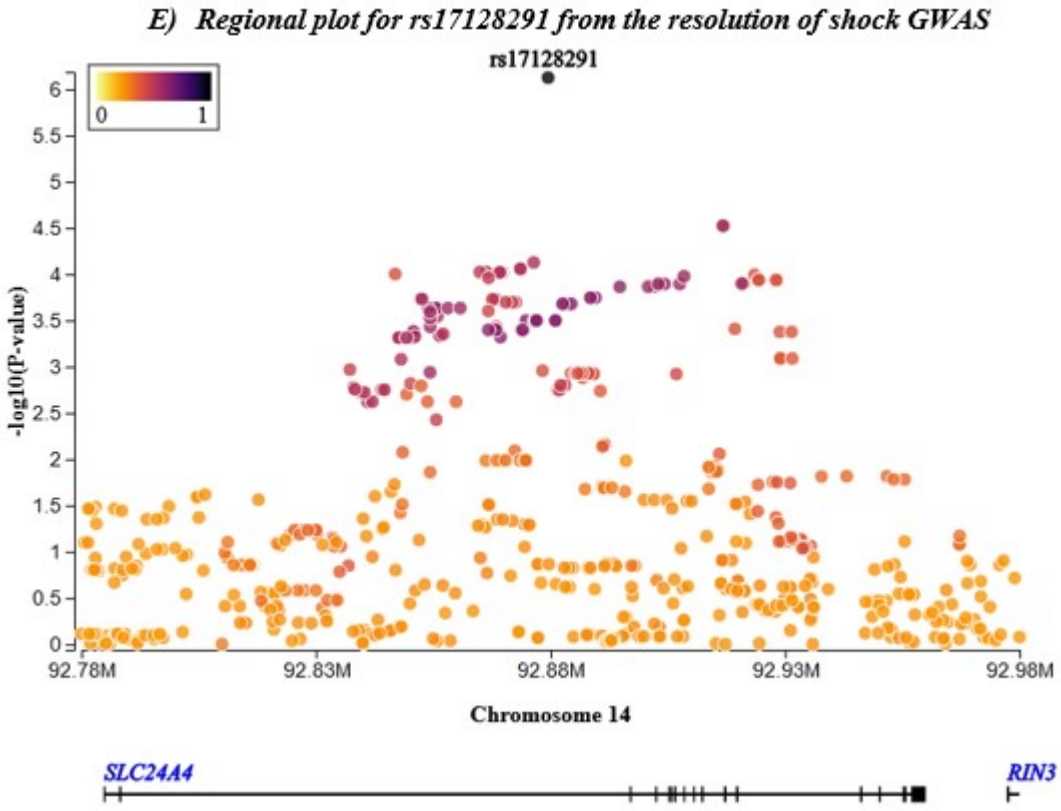


C) Regional plot for rs368584 from the 28-day mortality GWAS

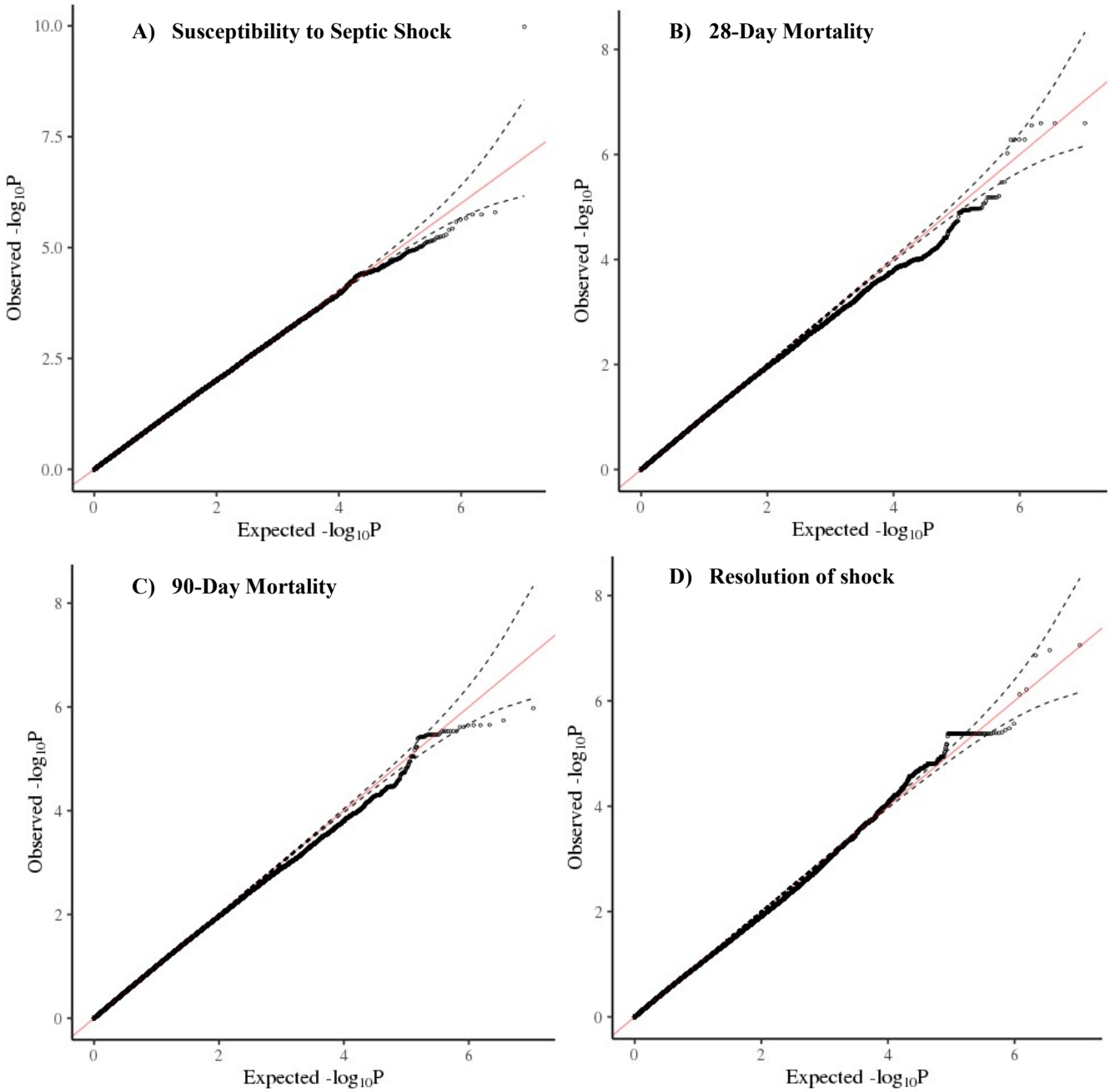


D) Regional plot for rs7698838 from the resolution of shock GWAS





Supplementary Figure S4. Regional Plots for the Genome-Wide and Suggestively Significant Associated Single Nucleotide Polymorphisms (SNPs) A) rs9489328, B) rs11167801, C) rs368584, D) rs7698838, and E) rs17128291. Plotted are SNPs and genes within the 100kb surrounding regions. SNPs are coloured according to the pairwise linkage disequilibrium (R^2 compared to the lead SNP calculated in European population in the 1000 Genomes Project). Blue genes are on the forward strand and red on the reverse. The plots were generated using LocusTrack implemented through the Complex-Trait Genetics Virtual Lab (Cuéllar-Partida et al., 2019). Note that the gene annotations are according the hg19 genome assembly, which explains why the SNP rs9489328 does not appear within *AL589740·1*, as stated in the results (hg38 build).



Supplementary Figure S5. Quantile-Quantile Plots for each Genome-Wide Association Study (GWAS). Comparison of the expected $-\log_{10}$ p-values expected under a null distribution to the observed GWAS values (susceptibility to septic shock (A), 28-day mortality (B), 90-day mortality (C), and resolution of shock (D). The dotted line represents the pointwise 95% confidence interval for what is expected if the data is normally distributed.

Supplementary Table S2. Genomic Inflation Factors (Lambda) for each GWAS

Phenotype	Lambda
Susceptibility to septic shock	1·025
28-day mortality	1·000
90-day mortality	1·009
Shock resolution	0·911

Supplementary Table S3. Tests of Previously Associated Single Nucleotide Polymorphisms (SNPs) in 28-Day Mortality Sepsis Genome-Wide Association Study (GWAS).

Study	SNP	Position	Minor Allele	Major Allele	MAF	Literature		Replication in ADRENAL-	
						P-Value	Odds Ratio	P-Value	Odds Ratio
A)	rs10928450	2:134086271	G	A	0·240	$9·00 \times 10^{-6}$	0·630	0·437	1·167
	rs146730869	1:82383883	A	G	0·015	$5·30 \times 10^{-6}$	4·480	0·612	1·409
	rs17057959	13:38969457	C	T	0·160	$1·50 \times 10^{-6}$	1·780	0·063	0·606
	rs35947027	7:123248738	G	A	0·312	$7·60 \times 10^{-6}$	1·540	0·476	0·873
	rs4732529	7:83635586	T	C	0·156	$1·60 \times 10^{-6}$	1·780	0·317	0·784
	rs4957796	5:108402140	C	T	0·174	$9·70 \times 10^{-8}$	0·520	0·925	0·979
	rs62375529	5:108417332	C	T	0·181	$7·50 \times 10^{-7}$	0·560	0·445	0·836
	rs639405	5:134532593	A	T	0·263	$8·00 \times 10^{-6}$	0·620	0·847	1·039
	rs72661871	4:91619360	A	G	0·046	$7·80 \times 10^{-6}$	2·870	0·095	1·842
	rs72661895	4:91671916	G	A	0·045	$6·40 \times 10^{-6}$	2·920	0·084	1·883
	rs76881522	7:83670129	A	T	0·129	$6·20 \times 10^{-6}$	1·770	0·519	0·848
	rs77054842	6:103813490	G	A	0·076	$7·30 \times 10^{-6}$	2·060	0·799	1·083
	rs79423885	6:103810003	G	A	0·076	$8·10 \times 10^{-6}$	2·050	0·799	1·083
	rs893357	2:201308486	C	T	0·053	$3·40 \times 10^{-6}$	2·700	0·259	1·503
	rs9566343	13:39102184	G	T	0·188	$1·40 \times 10^{-6}$	1·710	0·263	0·770
	rs975056	5:108406299	C	T	0·213	$3·30 \times 10^{-7}$	0·560	0·586	0·887
B)*	rs112692056	10:95820702	T	C	0·053	$3·30 \times 10^{-6}$	2·200	0·120	1·727
	rs114618137	5:113387846	C	T	0·111	$2·70 \times 10^{-6}$	1·800	0·658	1·123
	rs117914209	18:51427254	C	T	0·023	$6·50 \times 10^{-6}$	2·960	0·392	0·591
	rs2096460	21:33704100	C	A	0·105	$8·10 \times 10^{-6}$	0·610	0·394	0·776
	rs2709532	2:133426183	G	C	0·439	$3·80 \times 10^{-6}$	0·710	0·748	0·945
	rs4732529	7:83635586	T	C	0·156	$1·80 \times 10^{-6}$	1·590	0·317	0·784
	rs6501341	17:67665781	G	A	0·083	$3·50 \times 10^{-6}$	1·980	0·970	0·988
	rs74438932	13:27422997	T	A	0·074	$1·10 \times 10^{-6}$	1·900	0·812	1·080
	rs78690211	3:134815187	T	A	0·078	$1·30 \times 10^{-6}$	1·990	0·400	0·751
	rs942635	6:163602261	T	C	0·151	$6·90 \times 10^{-6}$	1·540	0·412	1·200
	rs9876830	3:157311299	A	G	0·319	$7·30 \times 10^{-6}$	1·420	0·786	0·953

C)	rs10933728	3:194027568	G	A	0·031	$5{\cdot}62 \times 10^{-6}$	7·000	0·558	1·308
	rs115550031	4:856102	A	G	0·020	$2{\cdot}45 \times 10^{-6}$	13·800	0·452	1·509
	rs117983287	9:80020874	A	C	0·010	$8{\cdot}16 \times 10^{-8}$	18·200	0·529	0·501
	rs150062338	3:188004948	T	C	0·010	$2{\cdot}32 \times 10^{-7}$	38·600	0·367	1·907
	rs150811371	12:23661042	A	G	0·099	$2{\cdot}93 \times 10^{-6}$	3·400	0·365	0·746
	rs2641697	16:84885777	G	C	0·350	$5{\cdot}99 \times 10^{-6}$	2·000	0·051	1·405
	rs382422	1:68916123	C	G	0·197	$3{\cdot}21 \times 10^{-6}$	2·100	0·235	0·761
	rs58764888	3:11217691	A	T	0·016	$6{\cdot}70 \times 10^{-7}$	13·300	0·643	1·330
	rs62369989	5:117409248	G	T	0·271	$7{\cdot}98 \times 10^{-6}$	2·100	0·768	0·947
	rs7211184	17:14257083	G	C	0·298	$9{\cdot}43 \times 10^{-6}$	2·000	0·632	1·089
	rs72862231	3:37853059	A	T	0·054	$1{\cdot}73 \times 10^{-6}$	4·400	0·680	0·849
	rs409443 †	6:33000554	T	C	0·460	$2{\cdot}21 \times 10^{-6}$	16·200	0·880	1·095
	rs9529561	13:69899506	G	A	0·093	$3{\cdot}34 \times 10^{-7}$	3·900	0·182	1·421

Summary statistics were extracted from A) European patients with sepsis caused by pneumonia (Supplementary Table 3 of Rautanen et al., 2015), B) European patients with sepsis caused by pneumonia or abdominal infections (Supplementary Table 4 of Rautanen et al., 2015), and C) 28 day mortality in European patients with sepsis Table 2 and Table 3 of Scherag et al., 2016). Listed are the SNP identifiers, discovery p-values from the literature, position in the genome (chromosome: base pair position), minor/effect allele, major/non-effect allele, frequency of the minor allele (MAF) in the ADRENAL-GWAS cohort, and p-values from the 28-day mortality GWAS. The odds ratio is in reference to the minor allele in both the original GWAS and the ADRENAL-GWAS GWAS.

*The odds ratio from Rautanen et al reflect survival as opposed to mortality, so an inverse effect is expected in the 28-day mortality replication.

†The rs409443 SNP was previously known as rs115036193 (and published in this way in the previous paper).

Supplementary Table S4. Tests of Previously Associated Single Nucleotide Polymorphisms (SNPs) in Susceptibility to Sepsis Genome-Wide Association Study (GWAS).

Study	SNP	Position	Minor Allele	Major Allele	MAF	Literature		Replication	
						P-Value	Odds Ratio	P-Value	Odds Ratio
D)	rs13380717	16:86904135	G	A	0·247	$1{\cdot}1 \times 10^{-7}$	-*	0·816	1·044
	rs2412930	4:59588228	A	G	0·134	$1{\cdot}2 \times 10^{-6}$	-	0·210	1·330
	rs34528289	16:86907297	T	C	0·193	$7{\cdot}0 \times 10^{-7}$	-	0·814	1·049
	rs41461846	2:219313354	C	T	0·387	$1{\cdot}9 \times 10^{-6}$	-	0·850	0·969
	rs59876150	16:86918734	C	G	0·330	$6{\cdot}8 \times 10^{-7}$	-	0·654	1·080
	rs6717433	2:219375711	C	G	0·388	$2{\cdot}0 \times 10^{-6}$	-	0·795	0·958
	rs6837629	4:59583956	C	T	0·133	$1{\cdot}5 \times 10^{-6}$	-	0·186	1·352
	rs72965151 †	2:219344165	T	G	0·389	$2{\cdot}0 \times 10^{-6}$	-	0·777	0·954
	rs9456883	6:164200021	C	T	0·453	$1{\cdot}6 \times 10^{-6}$	-	0·741	0·948
	rs9933616	16:86903194	G	A	0·194	$3{\cdot}6 \times 10^{-7}$	-	0·640	1·099
E)	rs75667310	6:36689198	A	T	0·015	$3{\cdot}05 \times 10^{-9}$	1·004	0·341	0·522
	rs74648178	6:36671178	A	G	0·014	$1{\cdot}90 \times 10^{-7}$	1·004	0·438	0·588
	rs41267779	6:160147058	C	G	0·052	$8{\cdot}15 \times 10^{-7}$	1·002	0·427	1·320
	rs75601073	2:59364237	G	A	0·021	$9{\cdot}01 \times 10^{-7}$	1·003	0·947	1·040
	rs71532474	8:120857083	G	A	0·060	$1{\cdot}16 \times 10^{-6}$	1·002	0·385	1·328
	rs79086515	7:78164937	G	A	0·015	$1{\cdot}24 \times 10^{-6}$	1·003	0·184	0·355
	rs4444770	4:80766054	A	G	0·154	$1{\cdot}38 \times 10^{-6}$	1·001	0·713	0·921
	rs114078858	1:201711585	T	C	0·017	$1{\cdot}44 \times 10^{-6}$	1·003	0·859	1·112
	rs56130537	6:160224203	G	A	0·050	$1{\cdot}51 \times 10^{-6}$	1·002	0·432	1·325
	rs7690505	4:80762635	C	T	0·155	$1{\cdot}64 \times 10^{-6}$	1·001	0·699	0·917
	rs61939273	12:130493235	A	G	0·111	$1{\cdot}67 \times 10^{-6}$	1·001	0·133	0·668
	rs138925664	20:7580820	A	G	0·014	$1{\cdot}82 \times 10^{-6}$	1·003	0·716	1·261
	rs1466515	4:156514879	G	A	0·103	$2{\cdot}47 \times 10^{-6}$	0·999	0·619	1·139
	rs35981701	4:80791075	T	C	0·151	$2{\cdot}85 \times 10^{-6}$	1·001	0·646	0·901
	rs74307801	9:117057928	T	G	0·059	$2{\cdot}89 \times 10^{-6}$	0·998	0·715	1·131
	rs4690159	4:80781873	C	G	0·156	$2{\cdot}97 \times 10^{-6}$	1·001	0·675	0·911

	rs78535155	13:49435399	G	A	0·014	$3{\cdot}37 \times 10^{-6}$	1·003	0·956	1·037
	rs28535971	22:17664296	G	C	0·345	$3{\cdot}75 \times 10^{-6}$	1·001	0·170	1·258
	rs242323	21:28901549	G	A	0·147	$3{\cdot}81 \times 10^{-6}$	1·001	0·799	0·943
	rs259492	3:21939427	A	T	0·298	$3{\cdot}86 \times 10^{-6}$	1·001	0·388	1·164
	rs34497103	4:80710324	A	G	0·155	$4{\cdot}08 \times 10^{-6}$	1·001	0·817	0·950
	rs36066750	4:80730535	C	G	0·156	$4{\cdot}95 \times 10^{-6}$	1·001	0·769	0·937
	rs61406966	6:33049123	A	G	0·012	$5{\cdot}13 \times 10^{-6}$	1·003	0·438	1·672
	rs16868789	6:33072598	G	A	0·014	$5{\cdot}23 \times 10^{-6}$	1·003	0·330	1·810
	rs7136342	12:91431056	T	C	0·176	$5{\cdot}70 \times 10^{-6}$	0·999	0·271	1·256
	rs4356266	11:111162890	T	A	0·295	$5{\cdot}73 \times 10^{-6}$	1·001	0·122	1·309
	rs72646737	8:41321196	C	G	0·172	$6{\cdot}04 \times 10^{-6}$	0·999	0·223	1·288
	rs148092072	11:131511485	T	A	0·018	$6{\cdot}39 \times 10^{-6}$	1·003	0·780	0·836
	rs72740098	15:80532134	G	A	0·192	$6{\cdot}96 \times 10^{-6}$	1·001	0·279	1·238
	rs78009740	9:100479810	T	G	0·024	$7{\cdot}39 \times 10^{-6}$	1·002	0·547	0·730
	rs79500616	8:84157112	A	G	0·042	$7{\cdot}80 \times 10^{-6}$	0·998	0·862	0·931
	rs13146131	4:80633295	C	G	0·141	$8{\cdot}35 \times 10^{-6}$	1·001	0·540	0·868
	rs75678135	14:81043621	C	T	0·011	$8{\cdot}60 \times 10^{-6}$	1·004	0·863	1·136
	rs78934109	10:35900880	T	C	0·030	$9{\cdot}13 \times 10^{-6}$	1·002	0·897	1·063
	rs185052458	14:54609469	T	C	0·010	$9{\cdot}26 \times 10^{-6}$	1·003	0·333	2·082
	rs77032716	12:95153027	G	A	0·016	$9{\cdot}73 \times 10^{-6}$	1·003	0·089	2·743
F)	rs114965692	2:30637041	C	T	0·059	$5{\cdot}29 \times 10^{-7}$	1·001	0·502	0·790
	rs114349669	4:171783881	T	A	0·014	$8{\cdot}79 \times 10^{-10}$	1·002	0·278	0·427
	rs17000198	5:87634748	T	C	0·016	$3{\cdot}73 \times 10^{-9}$	1·001	0·568	1·427
	rs78219843	17:31170397	A	G	0·021	$3{\cdot}77 \times 10^{-8}$	1·001	0·688	1·243

Summary statistics were extracted from (D) extremely premature multi-racial and multi-ethnic infants with sepsis (Table 1 of Srinivasan et al., 2017), (E) 'other septicaemia' (Phecode_A41), and (F) 'septicaemia/sepsis infections' (Phecode_20002_1657) from the UK Biobank (Neale, 2018). Listed are the SNP identifiers, discovery p-values from the literature, position in the genome (chromosome:base pair position), minor/effect allele, major/non-effect allele, frequency of the minor allele (MAF) in the combined ADRENAL-QIMRB cohort, and p-values from the susceptibility to septic shock GWAS. The odds ratio is in reference to the minor allele in both the original GWAS and the ADRENAL-GWAS analyses.

*Srinivasan et al did not report the effect size of the genetic associations. † Srinivasan et al reported this SNP as rs72965151 (chr2:219344165), but it has since been renamed.

Supplementary Table S5. Top Five Prioritised Genes from the A) Susceptibility to Septic Shock, B) 28-Day Mortality, C) 90-Day Mortality, and D) Shock Resolution GWAS.

GWAS	Gene Symbol or ENSEMBL Gene ID	Chromosome and Position	Top SNP in Locus	Nominal P-Value
A)	*PCSK5*	9:78505560-78977255	rs7870046	0·013
	PRR15	7:29603427-29606911	rs10499588	0·053
	ABCA13	7:48211055-48687092	rs17712293	0·054
	COL13A1	10:71561644-71724031	rs3847353	0·059
	ENSG00000245622	4:119585252-119759838	rs7670182	0·064
B)	*ZSCAN5A*	19:56732681-56826294	rs10420747	0·194
	PRDM10	11:129685714-129872730	rs491027	0·200
	MICAL2	11:12115543-12285334	rs12794303	0·274
	CMYA5	5:78985700-79096063	rs259074	0·311
	NFRKB	11:129685714-129872730	rs491027	0·317
C)	*SPTLC3*	20:12989627-13147411	rs13042895	0·002
	C11orf63	11:122709208-122830506	rs3741016	0·009
	DNAH7	2:196440701-196935730	rs17180544	0·023
	DSCAM	21:38437942-43816955	rs2837413	0·059
	ENSG00000246662	8:94225531-94712661	rs13257578	0·093
D)	*GYPA*	4:144257915-145061904	rs13123634	0·191
	RIMS1	6:72596406-73112845	rs1147531	0·210
	ENSG00000246896	19:15050246-16748905	rs28371512	0·210
	GYPB	4:144257915-145061904	rs13123634	0·261
	ENSG00000245067	4:57975928-58071676	rs7698838	0·276

Reported are the gene symbols or ENSEMBL gene IDs, position in the genome, the top SNP in the region, and the nominal p-values as reported by DEPICT in the Complex-Traits Genetics Virtual Lab. All have a false discovery rate > 5%.

Supplementary Table S6. Top Five Enriched Pathways from the A) Susceptibility to Septic Shock, B) 28-Day Mortality, C) 90-Day Mortality, and D) Shock Resolution GWAS.

GWAS	Gene Set ID	Gene Set Description	Nominal P-Value
A)	ENSG00000164134	*NAA15* subnetwork	$1{\cdot}05 \times 10^{-4}$
	ENSG00000150768	*DLAT* subnetwork	$1{\cdot}63 \times 10^{-4}$
	ENSG00000109220	*CHIC2* subnetwork	$2{\cdot}95 \times 10^{-4}$
	GO:0022408	Negative regulation of cell-cell adhesion	$2{\cdot}96 \times 10^{-4}$
	ENSG00000138363	*ATIC* subnetwork	$3{\cdot}05 \times 10^{-4}$
B)	REACTOME_PYRUVATE_METABOLISM_AND_CITRIC_ACID_TCA_CYCLE	Reactome pyruvate metabolism and citric acid TCA cycle	$2{\cdot}02 \times 10^{-5}$
	MP:0005533	Increased body temperature	$6{\cdot}34 \times 10^{-5}$
	MP:0000811	Hippocampal neuron degeneration	$1{\cdot}01 \times 10^{-4}$
	REACTOME_CITRIC_ACID_CYCLE_TCA_CYCLE	Reactome citric acid cycle TCA cycle	$1{\cdot}22 \times 10^{-4}$
	ENSG00000100320	*RBFOX2* subnetwork	$2{\cdot}14 \times 10^{-4}$
C)	GO:0010634	Positive regulation of epithelial cell migration	$1{\cdot}09 \times 10^{-4}$
	GO:0034706	Sodium channel complex	$1{\cdot}22 \times 10^{-4}$
	GO:0050885	Neuromuscular process controlling balance	$2{\cdot}09 \times 10^{-4}$
	ENSG00000175189	*INHBC* subnetwork	$4{\cdot}04 \times 10^{-4}$
	GO:0002244	Hemopoietic progenitor cell differentiation	$4{\cdot}15 \times 10^{-4}$
D)	MP:0001883	Mammary adenocarcinoma	$3{\cdot}04 \times 10^{-6}$
	GO:0005916	Fascia adherens	$2{\cdot}07 \times 10^{-5}$
	GO:0044291	Cell-cell contact zone	$1{\cdot}41 \times 10^{-4}$
	GO:0009314	Response to radiation	$1{\cdot}47 \times 10^{-4}$
	MP:0011204	Abnormal visceral yolk sac blood island morphology	$1{\cdot}63 \times 10^{-4}$

Reported are the gene set or reactome IDs, descriptions of the gene-set, and nominal p-values as reported by DEPICT in the Complex-Traits Genetics Virtual Lab. All have a false discovery rate > 5%.

Supplementary Table S7. Top Five Enriched Tissues from the A) Susceptibility to Septic Shock, B) 28-Day Mortality, C) 90-Day Mortality, and D) Shock Resolution GWAS.

GWAS	MeSH Term	MeSH First Level Term	MeSH Second Level Term	Nominal P-Value
A)	A07.231.908	Veins	Cardiovascular System	0·012
	A07.231.908.670.874	Umbilical Veins	Cardiovascular System	0·013
	A07.231.908.670	Portal System	Cardiovascular System	0·013
	A07.231	Blood Vessels	Cardiovascular System	0·021
	A03.734.414	Islets of Langerhans	Digestive System	0·024
B)	A03.556.124.369	Intestinal Mucosa	Digestive System	0·014
	A03.556	Gastrointestinal Tract	Digestive System	0·019
	A03.556.124	Intestines	Digestive System	0·032
	A07.541.510.110	Aortic Valve	Cardiovascular System	0·042
	A07.541.510	Heart Valves	Cardiovascular System	0·042
C)	A11.872.190	Embryonic Stem Cells	Cells	0·010
	A11.872.700	Pluripotent Stem Cells	Cells	0·010
	A11.872.700.500	Induced Pluripotent Stem Cells	Cells	0·010
	A11.872.040	Adult Stem Cells	Cells	0·021
	A05.360.319.114.373	Fallopian Tubes	Urogenital System	0·025
D)	A05.360.444.492.362	Foreskin	Urogenital System	0·045
	A05.360.444.492	Penis	Urogenital System	0·051
	A08.186	Central Nervous System	Nervous System	0·051
	A08.186.211	Brain	Nervous System	0·053
	A08.186.211.730.885.287.249	Basal Ganglia	Nervous System	0·064

Reported are the Medical SubHeading (MeSH) terms, and nominal p-values as reported by DEPICT in the Complex-Traits Genetics Virtual Lab. All have a false discovery rate > 5%.

Discussion S1. Lead SNP

The lead SNP rs9489328 has many correlated nearby variants (in linkage disequilibrium), which are expected to be inflated in the susceptibility to shock GWAS. The lead SNP was queried using LDproxy, and the correlated SNPs ($R^2 > 0.5$) were investigated (Machiela & Chanock, 2015). Given the SNP had passed all QC steps and was genotyped rather than imputed, and the nearby SNPs do not display association (Supplementary Table S7) it is possible that this SNP association is a false positive due to batch effects.

Supplementary Table S8. Single Nucleotide Polymorphisms (SNPs) in Linkage Disequilibrium ($R^2 > 0.5$) with the Lead Variant rs9489328 in the Susceptibility to Septic Shock Genome-Wide Association Study (GWAS).

SNP	Chromosome: Base Position	Minor Allele	Major Allele	MAF ADRENAL-GWAS*	MAF QIMRB	P-Value
rs9385020	6:98036720	G	A	0·124	0·129	0·598
rs4391266	6:98044632	G	A	0·124	0·129	0·611
rs10457321	6:98047483	A	G	0·124	0·131	0·474
rs12174940	6:98056560	T	C	0·124	0·132	0·456
rs12214244	6:98064504	G	A	0·124	0·132	0·456
rs9387519	6:98066707	G	A	0·124	0·132	0·456
rs9374687	6:98066803	C	G	0·124	0·132	0·456
rs9387520	6:98071180	A	C	0·123	0·130	0·506
rs9401038	6:98073606	C	G	0·124	0·132	0·456
rs10782190	6:98082488	T	C	0·125	0·132	0·509
rs10457325	6:98083452	T	C	0·125	0·132	0·509
rs9385037	6:98095781	G	A	0·125	0·131	0·541
rs12198339	6:98102334	A	G	0·122	0·129	0·468
rs12198387	6:98102358	A	G	0·122	0·129	0·478
rs9401061	6:98104498	G	A	0·152	0·160	0·378
rs9489328	**6:98104575**	**T**	**G**	**0·050**	**0·125**	**$1{\cdot}05 \times 10^{-10}$**
rs9401062	6:98107290	T	A	0·122	0·129	0·458
rs5028124	6:98107949	A	C	0·122	0·130	0·447
rs9372499	6:98107976	A	C	0·122	0·130	0·447
rs9385041	6:98108170	A	C	0·122	0·129	0·458
rs9401064	6:98108458	A	T	0·122	0·129	0·458
rs9372500	6:98109180	C	G	0·122	0·130	0·447
rs9387572	6:98110143	A	G	0·122	0·130	0·447

rs9374726	6:98111169	G	C	0·122	0·130	0·447
rs9372501	6:98112461	G	A	0·151	0·160	0·336
rs9401065	6:98113020	C	T	0·122	0·130	0·447
rs4368815	6:98113191	C	A	0·122	0·130	0·447
rs4629686	6:98113739	C	A	0·122	0·130	0·447
rs9374727	6:98114448	G	C	0·122	0·130	0·447
rs9401067	6:98115775	T	C	0·122	0·130	0·447
rs9401068	6:98115977	C	G	0·122	0·130	0·447
rs9385044	6:98118996	A	G	0·164	0·161	0·895
rs9387574	6:98120117	A	C	0·165	0·162	0·867
rs9401070	6:98120224	G	A	0·165	0·162	0·882
rs4288217	6:98120381	C	T	0·179	0·178	0·885
rs9481791	6:98120959	A	G	0·165	0·162	0·891
rs12209527	6:98120987	C	T	0·177	0·178	0·787
rs9387575	6:98121460	G	A	0·165	0·162	0·867
rs9387576	6:98121640	C	A	0·165	0·162	0·882
rs9401071	6:98122398	T	C	0·165	0·162	0·897
rs9385045	6:98124085	A	G	0·165	0·162	0·897
rs9385046	6:98124199	T	G	0·165	0·162	0·897
rs9387579	6:98124276	T	C	0·165	0·162	0·897
rs9387580	6:98124764	T	C	0·165	0·162	0·897
rs9387581	6:98124952	T	A	0·165	0·162	0·897
rs9385047	6:98124984	T	A	0·165	0·162	0·897
rs9387583	6:98125710	A	G	0·165	0·163	0·922
rs9385048	6:98127377	G	A	0·165	0·163	0·923
rs9489412	6:98128028	G	A	0·165	0·163	0·937
rs13194546	6:98129850	C	A	0·199	0·195	0·959
rs9374734	6:98130434	G	A	0·165	0·163	0·937
rs9401075	6:98130467	A	G	0·165	0·163	0·937
rs9387584	6:98130580	A	G	0·165	0·163	0·937
rs9387585	6:98131914	C	A	0·165	0·163	0·926
rs9398490	6:98132413	G	T	0·165	0·163	0·915
rs9489426	6:98132648	G	A	0·179	0·179	0·822
rs9387587	6:98133035	G	A	0·165	0·163	0·926
rs4292532	6:98133643	T	G	0·165	0·163	0·926
rs4298354	6:98133866	A	G	0·165	0·163	0·926
rs11153755	6:98134312	C	T	0·165	0·163	0·944
rs9387589	6:98134533	T	C	0·165	0·163	0·944
rs4295491	6:98136040	A	T	0·164	0·163	0·991
rs9387592	6:98136175	T	C	0·164	0·163	0·991
rs118178376	6:98136423	A	C	0·164	0·163	0·991
rs143443001	6:98136467	A	C	0·164	0·163	0·980
rs117401376	6:98136528	G	A	0·164	0·163	0·980
rs72925022	6:98136645	C	T	0·164	0·163	0·980
rs72925026	6:98136753	T	C	0·164	0·163	0·980

rs72925029	6:98136833	A	G	0·164	0·163	0·966
rs72925031	6:98136878	G	A	0·164	0·163	0·966
rs72925034	6:98137002	T	A	0·165	0·163	0·971
rs72925041	6:98137177	G	A	0·162	0·162	0·960
rs9385050	6:98137190	C	A	0·162	0·162	0·960
rs72925045	6:98137208	C	G	0·162	0·162	0·960
rs11153757	6:98137970	G	T	0·198	0·184	0·371
rs7450752	6:98138025	A	G	0·198	0·184	0·371
rs4145639	6:98138181	G	T	0·199	0·184	0·332
rs9401078	6:98138823	A	G	0·199	0·185	0·349
rs9401079	6:98139266	A	G	0·199	0·185	0·349
rs4263590	6:98139335	A	G	0·199	0·185	0·349
rs4628107	6:98139366	G	A	0·167	0·163	0·802
rs4620129	6:98139526	G	A	0·199	0·185	0·349
rs4467779	6:98139671	G	A	0·199	0·185	0·349
rs7744547	6:98140008	C	T	0·199	0·185	0·349
rs9374740	6:98140435	C	T	0·199	0·185	0·349
rs9489476	6:98141965	C	T	0·167	0·162	0·751
rs9374741	6:98145164	G	A	0·168	0·162	0·693
rs9374742	6:98145304	G	T	0·201	0·184	0·251
rs11153770	6:98147840	T	G	0·169	0·163	0·690
rs9387597	6:98152901	A	G	0·215	0·202	0·426
rs9401087	6:98156441	G	T	0·203	0·185	0·236
rs9398494	6:98158104	A	G	0·168	0·162	0·693
rs6936235	6:98160308	A	G	0·201	0·184	0·251
rs3920538	6:98160313	G	C	0·128	0·130	0·812
rs1159178	6:98160544	G	A	0·201	0·184	0·266
rs998115	6:98161192	C	T	0·204	0·185	0·219
rs9372514	6:98161937	G	T	0·168	0·162	0·693
rs9385058	6:98161954	A	G	0·201	0·184	0·258
rs9489538	6:98163545	T	C	0·201	0·184	0·258
rs9320668	6:98164450	A	G	0·197	0·183	0·376
rs1158724	6:98165021	A	G	0·189	0·175	0·369
rs9401107	6:98168794	A	G	0·156	0·153	0·891
rs9387620	6:98169324	T	C	0·201	0·192	0·641
rs9401109	6:98169381	A	G	0·158	0·155	0·880
rs9385065	6:98171275	C	T	0·169	0·167	0·904
rs9489575	6:98172953	T	C	0·130	0·134	0·662
rs9320674	6:98172980	G	A	0·129	0·137	0·475

*Throughout this table the minor allele frequency (MAF) corresponds to the minor allele which is also the effect allele from the GWAS.

Discussion S2. Suggestively Associated SNPs Discussion

Four SNPs, rs368584, rs11167801, rs7698838, and rs17128291, reached suggestive levels of significance in the GWAS. The SNP rs368584 lies within an intron of the *COL4A2* gene, which encodes a type 4 collagen. Variants within this gene have previously been genome-wide significantly associated with a number of phenotypes, as summarised in the GWAS Catalog, including diastolic blood pressure, coronary artery disease, leukocyte count, and glomerular filtration rate (MacArthur et al., 2017; Hoffmann et al., 2017; Kanai et al., 2018; van der Harst & Verweij, 2018; Kichaev et al., 2019). The SNP rs11167801 lies within an intron of *ARHGAP26,* which encodes the Rho GTPase activating protein 26, which plays a role in signalling cascades and organisation of the actin-cytoskeleton. Variants in this gene have been previously associated with coronary artery disease and eosinophil count, amongst others (van der Harst & Verweij, 2018; Kichaev et al., 2019). The SNP rs17128291 sits within an intron of *SLC24A4*, and the gene product is involved in potassium-dependent sodium/calcium exchange. Variants in this region been previously associated with a number of hair and eye colour phenotypes as well as Alzheimer's disease (Morgan et al., 2018; Sulem et al., 2007; Marioni et al., 2018). The final suggestive SNP association, rs7698838, sits in an intergenic region of the genome, and has not been previously associated with any phenotypes.

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