## SUPPLEMENTAL MATERIAL TABLE OF CONTENTS

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**Supplemental Table 1: Hazard Ratios* (HRs) and 95% Confidence Intervals (CIs) for the association between *APOL1* genotype and incident sepsis in blacks in the REGARDS Study adjusting for the development of end-stage kidney disease prior to sepsis**

| | | Sepsis HR (95% CI) | | | |
|---|---|---|---|---|---|
| ***APOL1* Risk Genotype** | **No. Events (%)‡** | **Adjusted Model** | **Adjusted Model + Mediator** | **Ancestry Adjusted Model** | **Ancestry adjusted Model + Mediator** |
| *Recessive Model* | | | | | |
| 0 or 1 risk allele | 242(2.7) | - | - | - | |
| 2 risk alleles | 42(3.2) | 1.15(0.80-1.65) | 1.14(0.80-1.64) | 0.98(0.63-1.53) | 1.00(0.64-1.56) |
| *Dominant Model* | | | | | |
| 0 risk alleles | 98(2.3) | - | - | | |
| 1 or 2 risk alleles | 186(3.1) | 1.38(1.06-1.80) | 1.37(1.05-1.79) | 1.45(1.05-2.00) | 1.44(1.04-1.99) |
| *Additive Model* | | | | | |
| per variant allele copy | 284(2.8) | 1. 22(1.01-1.46) | 1.21(1.01-1.45) | 1.19(0.96-1.48) | 1.20(0.96-1.49) |

*Estimated from Cox proportional hazard models.
‡Row percentage, proportion of participants experiencing a sepsis event (Total $N$ = 306); number of ESKD events (Total $N$ = 300, among sepsis $N$ = 35, among non-sepsis $N$ = 265); 22 sepsis events excluded as ESKD events occurred after sepsis events.
Adjusted Model includes sex, age, income, education, tobacco, deep vein thrombosis, dyslipidemia, peripheral artery disease, estimated glomerular filtration rate, albumin to creatinine ratio, systolic blood pressure, diastolic blood pressure, prevalent comorbidities (diabetes, coronary heart disease, stroke, dyslipidemia).
Ancestry adjusted Model includes Adjusted Model + adjusted for principal components of ancestry
Mediator: ESKD evens

**Supplemental Table 2: Odds Ratios* (ORs) and associated 95% Confidence Intervals (CIs) for the association between *APOL1* risk genotype group and incident 30-day sepsis mortality in blacks with sepsis (*N*=306)**

| *APOL1* Risk Genotype | No. Events (%)‡ | Sepsis Death OR (95% CI) | | |
|---|---|---|---|---|
| | | Crude | Model 1 | Model 2 |
| *Recessive Model* | | | | |
| 0 or 1 risk allele | 34(18.3) | - | - | - |
| 2 risk alleles | 8(25.0) | 1.49(0.62-3.60) | 1.94(0.73-5.14) | 1.77(0.50-6.32) |
| *Dominant Model* | | | | |
| 0 risk alleles | 10(13.3) | - | - | - |
| 1 or 2 risk alleles | 32(22.4) | 1.87(0.86-4.06) | 1.67(0.73-3.80) | 2.48(0.83-7.38) |
| *Additive Model* | | | | |
| per variant allele copy | 42(19.3) | 1.50(0.91-2.47) | 1.56(0.89-2.73) | 1.84(0.89-3.79) |

Estimated from Cox proportional hazard models.
‡Row percentage, proportion of participants experiencing a sepsis 30-day mortality event
Model 1: adjusted for sex, age, income, education
Model 2: Model 1 + adjusted for tobacco, deep vein thrombosis, dyslipidemia, peripheral artery disease, estimated glomerular filtration rate, albumin to creatinine ratio, systolic blood pressure, diastolic blood pressure, prevalent comorbidities (diabetes, coronary heart disease, stroke, dyslipidemia).

**Supplemental Table 3: Hazard Ratios* and associated 95% Confidence Intervals for the association between G1 dominant *APOL1* risk genotype group and incident sepsis among blacks overall and stratified by diabetes and CKD**

| *APOL1* Risk Genotype | No. Events (%)‡ | Sepsis HR (95% CI) | | | |
|---|---|---|---|---|---|
| | | Crude | Model 1 | Model 2 | Model 3 |
| *G1 Dominant Model* | | | | | |
| 0 risk allele | 101(2.3) | - | - | - | |
| 1 or 2 risk alleles | 122(3.5) | 1.50(1.16-1.96) | 1.51(1.16-1.97) | 1.54(1.16-2.04) | 1.58(1.13-2.28) |
| *Diabetes* | | | | | |
| 0 risk allele | 48(3.7) | - | - | - | |
| 1 or 2 risk alleles | 69(6.5) | 1.74(1.20-2.52) | 1.73(1.19-2.51) | 1.75(1.17-2.62) | 1.52(0.94-2.46) |
| *No diabetes* | | | | | |
| 0 risk allele | 53(1.7) | - | - | - | |
| 1 or 2 risk alleles | 53(2.2) | 1.34(0.87-2.07) | 1.36(0.88-2.11) | 1.48(0.93-2.36) | 1.94(1.10-3.42) |
| *CKD* | | | | | |
| 0 risk allele | 53(4.8) | - | - | - | |
| 1 or 2 risk alleles | 67(7.2) | 1.44(1.01-2.07) | 1.44(1.00-2.08) | 1.67(1.12-2.47) | 1.79(1.11-2.87) |
| *No CKD* | | | | | |
| 0 risk allele | 48(1.5) | - | - | - | |
| 1 or 2 risk alleles | 55(2.2) | 1.47(0.99-2.16) | 1.46(0.99-2.15) | 1.35(0.89-2.05) | 1.45(0.86-2.43) |

*Estimated from Cox proportional hazard models.
‡Row percentage, proportion of participants experiencing a sepsis event.
Model 1: adjusted for sex, age, income, education
Model 2: Model 1 + adjusted for tobacco, deep vein thrombosis, dyslipidemia, peripheral artery disease, estimated glomerular filtration rate, albumin to creatinine ratio, systolic blood pressure, diastolic blood pressure, prevalent comorbidities (diabetes [except for diabetes stratified models], coronary heart disease, stroke, dyslipidemia).
Model 3: Model 2 + adjusted for principal components of ancestry

**Supplemental Table 4: Hazard Ratios* and associated 95% Confidence Intervals for the association between G2 dominant *APOL1* risk genotype group and incident sepsis among blacks overall and stratified by diabetes and CKD**

| *APOL1* Risk Genotype | No. Events (%)‡ | Sepsis HR (95% CI) | | | |
|---|---|---|---|---|---|
| | | Crude | Model 1 | Model 2 | Model 3 |
| *G2 Dominant Model* | | | | | |
| 0 risk allele | 101(2.3) | - | - | - | |
| 1 or 2 risk alleles | 65(3.2) | 1.37(1.00-1.87) | 1.42(1.04-1.94) | 1.49(1.06-2.07) | 1.69(1.13-2.53) |
| *Diabetes* | | | | | |
| 0 risk allele | 48(3.7) | - | - | - | |
| 1 or 2 risk alleles | 32(5.1) | 1.38(0.88-2.16) | 1.48(0.94-2.32) | 1.47(0.90-2.40) | 1.60(0.89-2.87) |
| *No diabetes* | | | | | |
| 0 risk allele | 53(1.7) | - | - | - | |
| 1 or 2 risk alleles | 33(2.4) | 1.34(0.87-2.07) | 1.36(0.88-2.11) | 1.48(0.93-2.36) | 1.94(1.10-3.42) |
| *CKD* | | | | | |
| 0 risk allele | 53(4.8) | - | - | - | |
| 1 or 2 risk alleles | 36(7.1) | 1.47(0.96-2.24) | 1.49(0.98-2.29) | 1.77(1.12-2.79) | 1.85(1.05-3.26) |
| *No CKD* | | | | | |
| 0 risk allele | 48(1.5) | - | - | - | |
| 1 or 2 risk alleles | 29(1.9) | 1.28(0.81-2.03) | 1.33(0.84-2.11) | 1.32(0.80-2.17) | 1.73(0.96-3.14) |

*Estimated from Cox proportional hazard models.
‡Row percentage, proportion of participants experiencing a sepsis event.
Model 1: adjusted for sex, age, income, education
Model 2: Model 1 + adjusted for tobacco, deep vein thrombosis, dyslipidemia, peripheral artery disease, estimated glomerular filtration rate, albumin to creatinine ratio, systolic blood pressure, diastolic blood pressure, prevalent comorbidities (diabetes [except for diabetes stratified models], coronary heart disease, stroke, dyslipidemia).
Model 3: Model 2 + adjusted for principal components of ancestry

**Supplemental Table 5: Hazard Ratios* and 95% Confidence Intervals for the association between G1 and G2 Additive Models of *APOL1* genotype and incident sepsis among blacks overall and stratified by diabetes and CKD**

| *APOL1* Risk Genotype | No. Events (%)‡ | Sepsis HR (95% CI) | | | |
|---|---|---|---|---|---|
| | | Crude | Model 1 | Model 2 | Model 3 |
| *G1 Additive Model* | | | | | |
| Full Cohort | 223/7771 | 1.35(1.11-1.65) | 1.37(1.13-1.68) | 1.41(1.14-1.75) | 1.38(1.07-1.78) |
| Diabetes | 117/2359 | 1.54(1.18-2.02) | 1.55(1.18-2.04) | 1.59(1.18-2.14) | 1.39(0.98-1.99) |
| No Diabetes | 106/5387 | 1.17(0.87-1.56) | 1.19(0.89-1.60) | 1.25(0.92-1.71) | 1.40(0.96-2.04) |
| CKD | 120/2040 | 1.28(0.99-1.67) | 1.30(0.99-1.69) | 1.47(1.10-1.96) | 1.60(1.13-2.26) |
| No CKD | 103/5731 | 1.34(0.99-1.79) | 1.35(1.00-1.81) | 1.29(0.94-1.79) | 1.21(0.81-1.82) |
| *G2 Additive Model* | | - | - | - | |
| Full Cohort | 166/6357 | 1.30(1.01-1.68) | 1.34(1.03-1.73) | 1.36(1.04-1.78) | 1.51(1.11-2.07) |
| Diabetes | 80/1923 | 1.30(0.90-1.86) | 1.36(0.95-1.96) | 1.35(0.92-1.99) | 1.48(0.94-2.33) |
| No Diabetes | 86/4412 | 1.28(0.98-1.84) | 1.31(0.91-1.88) | 1.36(0.93-2.01) | 1.71(1.09-2.70) |
| CKD | 89/1608 | 1.28(0.91-1.81) | 1.30(0.92-1.84) | 1.45(1.01-2.09) | 1.50(0.96-2.33) |
| No CKD | 77/4749 | 1.31(0.90-1.91) | 1.35(0.93-1.98) | 1.34(0.89-2.02) | 1.73(1.07-2.78) |

*Estimated from Cox proportional hazard models.
‡Row percentage, proportion of participants experiencing a sepsis event.
Model 1: adjusted for sex, age, income, education
Model 2: Model 1 + adjusted for tobacco, deep vein thrombosis, dyslipidemia, peripheral artery disease, estimated glomerular filtration rate, albumin to creatinine ratio, systolic blood pressure, diastolic blood pressure, prevalent comorbidities (diabetes [except for diabetes stratified models], coronary heart disease, stroke, dyslipidemia).
Model 3: Model 2 + adjusted for principal components of ancestry

**Supplemental Table 6: Hazard Ratios* and associated 95% Confidence Intervals for the association between G1 recessive *APOL1* risk genotype group and incident sepsis among blacks overall and stratified by diabetes and CKD**

| *APOL1* Risk Genotype | No. Events (%)‡ | Sepsis HR (95% CI) | | | |
|---|---|---|---|---|---|
| | | Crude | Model 1 | Model 2 | Model 3 |
| *G1 Recessive Model* | | | | | |
| 0 or 1 risk allele | 202(2.8) | - | - | - | |
| 2 risk alleles | 21(3.9) | 1.40(0.89-2.19) | 1.46(0.93- 2.29) | 1.61(1.01-2.57) | 1.31(0.72-2.38) |
| *Diabetes* | | | | | |
| 0 or 1 risk allele | 104(4.7) | - | - | - | |
| 2 risk alleles | 13(8.0) | 1.76(0.99-3.13) | 1.80(1.01-3.21) | 1.98(1.07-3.67) | 1.59(0.74-3.41) |
| *No diabetes* | | | | | |
| 0 or 1 risk allele | 98(2.0) | - | - | - | |
| 2 risk alleles | 8(2.1) | 1.07(0.52-2.21) | 1.13(0.55 -2.33) | 1.25(0.60-2.60) | 0.90(0.32-2.51) |
| *CKD* | | | | | |
| 0 or 1 risk allele | 108(5.7) | - | - | - | |
| 2 risk alleles | 12(7.4) | 1.24(0.68-2.25) | 1.27(0.70-2.32) | 1.59(0.86-2.94) | 1.90(0.93-3.89) |
| *No CKD* | | | | | |
| 0 or 1 risk allele | 94(1.8) | - | - | - | |
| 2 risk alleles | 9(2.4) | 1.38(0.70-2.74) | 1.44(0.73-2.86) | 1.49(0.72-3.10) | 0.75(0.23-2.43) |

*Estimated from Cox proportional hazard models.

‡Row percentage, proportion of participants experiencing a sepsis event.

Model 1: adjusted for sex, age, income, education

Model 2: Model 1 + adjusted for tobacco, deep vein thrombosis, dyslipidemia, peripheral artery disease, estimated glomerular filtration rate, albumin to creatinine ratio, systolic blood pressure, diastolic blood pressure, prevalent comorbidities (diabetes [except for diabetes stratified models], coronary heart disease, stroke, dyslipidemia).

Model 3: Model 2 + adjusted for principal components of ancestry

**Supplemental Table 7: Hazard Ratios* and associated 95% Confidence Intervals for the association between G2 recessive *APOL1* risk genotype group and incident sepsis among blacks overall and stratified by diabetes and CKD**

| *APOL1* Risk Genotype | No. Events (%)‡ | Sepsis HR (95% CI) | | | |
|---|---|---|---|---|---|
| | | Crude | Model 1 | Model 2 | Model 3 |
| *G2 Recessive Model* | | | | | |
| 0 or 1 risk allele | 158(2.6) | - | - | - | |
| 2 risk alleles | 8(3.7) | 1.41(0.69-2.88) | 1.43(0.70-2.92) | 1.32(0.62-2.85) | 1.69(0.76-3.72) |
| *Diabetes* | | | | | |
| 0 or 1 risk allele | 76(4.1) | - | - | - | |
| 2 risk alleles | 4(5.6) | 1.35(0.49-3.68) | 1.40(0.51-3.86) | 1.40(0.50-3.92) | 1.86(0.64-5.46) |
| *No diabetes* | | | | | |
| 0 or 1 risk allele | 82(1.9) | - | - | - | |
| 2 risk alleles | 4(2.8) | 1.40(0.51-3.81) | 1.49(0.55-4.08) | 1.26(0.39-4.08) | 1.96(0.59-6.46) |
| *CKD* | | | | | |
| 0 or 1 risk allele | 86(5.6) | - | - | - | |
| 2 risk alleles | 3(4.8) | 0.86(0.27-2.71) | 0.87(0.27-2.78) | 0.91(0.28-2.99) | 1.09(0.31-3.85) |
| *No CKD* | | | | | |
| 0 or 1 risk allele | 72(1.6) | - | - | - | |
| 2 risk alleles | 5(3.2) | 2.02(0.82-4.99) | 2.11(0.85-5.24) | 2.04(0.73-5.65) | 3.03(1.04-8.81) |

*Estimated from Cox proportional hazard models.

‡Row percentage, proportion of participants experiencing a sepsis event.

Model 1: adjusted for sex, age, income, education

Model 2: Model 1 + adjusted for tobacco, deep vein thrombosis, dyslipidemia, peripheral artery disease, estimated glomerular filtration rate, albumin to creatinine ratio, systolic blood pressure, diastolic blood pressure, prevalent comorbidities (diabetes [except for diabetes stratified models], coronary heart disease, stroke, dyslipidemia).

Model 3: Model 2 + adjusted for principal components of ancestry

**Supplemental Table 8: Type of organ dysfunction across *APOL1* models among sepsis participants**

| | Type of Organ Dysfunctions N (Percent) | | | | | |
|---|---|---|---|---|---|---|
| | **Kidney** | **Respiratory** | **Cardiovascular** | **Hepatic** | **Neurologic** | **Hematologic** |
| Recessive | | | | | | |
| 0 or 1 risk allele | 217(83.8%) | 58(22.4%) | 86(33.2%) | 61(23.5%) | 54(20.8%) | 68(26.2%) |
| 2 risk alleles | 42(80.4%) | 15(31.9%) | 12(25.5%) | 11(23.4%) | 7(14.9%) | 9(19.1%) |
| G1 Recessive | | | | | | |
| 0 or 1 risk allele | 174(86.1%) | 44(21.8%) | 70(34.6%) | 51(25.2%) | 40(19.8%) | 55(27.2%) |
| 2 risk alleles | 19(90.5%) | 8(38.1%) | 7(33.3%) | 2(9.5%) | 2(9.5%) | 3(14.3%) |
| G2 Recessive | | | | | | |
| 0 or 1 risk allele | 129(81.6%) | 36(22.8%) | 52(32.9%) | 32(20.2%) | 31(19.6%) | 41(25.9%) |
| 2 risk alleles | 7(87.5%) | 3(37.5%) | 1(12.5%) | 4(50.0%) | 3(37.5%) | 1(12.5%) |
| Dominant | | | | | | |
| 0 risk allele | 86(85.1%) | 22(21.8%) | 36(35.6%) | 22(21.8%) | 17(16.8%) | 28(27.7%) |
| 1 or 2 risk alleles | 173(84.4%) | 51(24.9%) | 62(30.2%) | 50(24.4%) | 44(21.5%) | 49(23.9%) |
| G1 Dominant | | | | | | |
| 0 risk allele | 86(85.1%) | 22(21.8%) | 36(35.6%) | 22(21.8%) | 17(16.8%) | 28(27.7%) |
| 1 or 2 risk alleles | 107(87.7%) | 30(24.6%) | 41(33.6%) | 31(25.4%) | 25(20.5%) | 30(24.6%) |
| G2 Dominant | | | | | | |
| 0 risk allele | 86(85.1%) | 22(21.8%) | 36(35.6%) | 22(21.8%) | 17(16.8%) | 28(27.7%) |
| 1 or 2 risk alleles | 50(76.9%) | 17(26.1%) | 53(26.1%) | 14(21.5%) | 17(26.1%) | 14(21.5%) |
| Additive | | | | | | |
| 0 risk allele | 86(85.1%) | 22(21.8%) | 36(35.6%) | 22(21.8%) | 17(16.8%) | 28(27.7%) |
| 1 risk allele | 131(82.9%) | 36(22.8%) | 50(31.6%) | 39(24.7%) | 37(23.4%) | 40(25.3%) |
| 2 risk alleles | 42(89.4%) | 15(31.9%) | 12(25.5%) | 11(23.4%) | 7(14.9%) | 9(19.1%) |

**Supplemental Table 9: Number of organ dysfunctions across *APOL1* models among sepsis participants**

| | Number of Organ Dysfunctions | | | |
|---|---|---|---|---|
| | **2** | **3** | **≥4** | **P value*** |
| Recessive | | | | |
| 0 or 1 risk allele | 104(40.1%) | 43(16.6%) | 112(43.2%) | 0.19 |
| 2 risk alleles | 18(38.3%) | 13(27.7%) | 26(34.0%) | |
| G1 Recessive | | | | 0.06 |
| 0 or 1 risk allele | 81(40.1%) | 28(13.9%) | 93(46.0%) | |
| 2 risk alleles | 6(28.6%) | 7(33.3%) | 8(38.1%) | |
| G2 Recessive | | | | 0.62 |
| 0 or 1 risk allele | 67(42.2%) | 30(19.0%) | 61(38.6%) | |
| 2 risk alleles | 2(25.0%) | 2(25.0%) | 4(50.0%) | |
| Dominant | | | | 0.47 |
| 0 risk allele | 44(43.6%) | 15(14.8%) | 42(41.6%) | |
| 1 or 2 risk alleles | 78(38.0%) | 41(20.0%) | 86(41.9%) | |
| G1 Dominant | | | | 0.44 |
| 0 risk allele | 44(43.6%) | 15(14.8%) | 42(41.6%) | |
| 1 or 2 risk alleles | 43(35.2%) | 20(16.4%) | 59(48.4%) | |
| G2 Dominant | | | | 0.20 |
| 0 risk allele | 44(43.6%) | 15(14.8%) | 42(41.6%) | |
| 1 or 2 risk alleles | 25(38.5%) | 17(26.1%) | 23(35.4%) | |
| Additive | | | | 0.36 |
| 0 risk allele | 44(43.6%) | 15(14.8%) | 42(41.6%) | |
| 1 risk allele | 60(38.0%) | 28(17.7%) | 70(44.3%) | |
| 2 risk alleles | 18(38.3%) | 13(27.7%) | 16(34.0%) | |

*P-value represents Chi-square test or Fisher Exact test as appropriate