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High CMV serology and subsequent COPD-related mortality: a longitudinal study

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Table S1 - Characteristics of TESAOD participants included and excluded from the current study

	Included (n=806)		Excluded (n=986)		p value†
	%	n/N*	%	n/N*	
Age‡	52.6 (51.8, 53.5)	806	49.4 (48.6, 50.2)	986	<0.0001
Sex					0.021
Women	60.2	485/806	54.8	540/986	
Men	30.8	321/806	45.2	446/986	
Body-mass index category					0.392
Underweight	1.9	15/784	3.3	20/609	
Normal weight	53.4	419/784	53.9	328/609	
Overweight	36.4	285/784	34.3	209/609	
Obese	8.3	65/784	8.5	52/609	
Smoking status					0.016
Never	37.5	302/805	35.5	344/970	
Former	27.6	222/805	23.3	226/970	
Current	34.9	281/805	41.2	400/970	
Education level					1.0
<12 years	61.5	496/806	61.5	600/975	
>12 years	38.5	310/806	38.5	375/975	
Airflow limitation**					0.752
Stage 0	85.6	690/806	85.9	534/622	
Stage 1	5.3	43/806	4.8	30/622	
Stage 2	7.0	56/806	6.4	40/622	
Stage 3+4	2.1	17/806	2.9	18/622	
MD Asthma					0.020
No	87.9	709/806	91.3	884/968	
Yes	12.3	97/806	8.7	84/968	
	Mean (95% CI)	N	Mean (95% CI)	N	
FEV₁ % predicted ‡	93.3 (92.0, 94.7)	806	94.0 (92.5, 95.5)	629	0.5081
FVC % predicted ‡	96.5 (95.3, 97.7)	806	97.2 (95.8, 98.6)	623	0.4624
FEV₁/FVC ratio ‡	78.9 (78.2, 79.6)	806	79.3 (78.5, 80.1)	623	0.3845
FEF₂₅₋₇₅ % predicted‡	89.4 (86.8, 91.9)	806	91.2 (88.3, 94.1)	623	0.3504
Pack-years ‡					
all	18.2 (16.6, 19.7)	805	18.5 (17.0, 20.0)	967	0.7392
only smokers	29.1 (27.1, 31.0)	503	28.7 (26.9, 30.6)	623	0.8255

**Airflow limitation: stage 0: FEV₁/FVC ratio \geq 70%, stage 1: FEV₁/FVC ratio < 70% and FEV₁ % predicted \geq 80%, stage 2: FEV₁/FVC ratio < 70% and FEV₁ % predicted 50-80%, stage 3+4: FEV₁/FVC ratio < 70% and FEV₁ % predicted <50%.

*Denominators vary depending on data completion.

† p-value based on Pearson Chi-square statistic unless otherwise indicated.

‡ data expressed as mean (95% CI), p-value based on Oneway ANOVA

Table S2: Associations of CMV, CP, and MP serology and of systemic inflammation with the risk of dying from or with COPD.

	HR (95% CI)* (N=783)	p
	Deaths=80	
CMV tertiles		
Medium	1.58 (0.82, 3.06)	0.171
High	2.56 (1.37, 4.78)	0.003
CP tertile		
Medium	0.85 (0.44, 1.62)	0.618
High	2.55 (1.48, 4.40)	0.001
MP tertile		
Medium	1.30 (0.74, 2.28)	0.360
High	1.29 (0.74, 2.25)	0.377
C-reactive protein (effect for 1-SD increase)	1.20 (0.93, 1.55)	0.163

* Cox model adjusted for age, sex, level of education, BMI categories, smoking status and pack year

Table S3: Associations between CMV tertiles and mortality by cardiovascular disease defined as underlying cause of death on death certificate (“from”; a) or as either underlying cause of death or co-existing condition on death certificate (“from or with”; b).

Mortality from cardiovascular disease (a)	All subjects (N=783)		<55 years (N=387)		≥ 55 years (N=396)	
	Deaths=274		Deaths=91		Deaths=183	
	HR (95% CI)	p	HR (95% CI)	p	HR (95% CI)	p
Low CMV tertile	reference		reference		reference	
Medium CMV tertile	0.95 (0.70, 1.29)	0.748	1.27 (0.78, 2.09)	0.338	0.70 (0.47, 1.04)	0.080
High CMV tertile	0.91 (0.66, 1.25)	0.562	1.14 (0.65, 2.02)	0.639	0.76 (0.52, 1.11)	0.151
Mortality from or with cardiovascular disease (b)	All subjects (N=783)		<55 years (N=387)		≥ 55 years (N=396)	
	Deaths=372		Deaths=133		Deaths=239	
	HR (95% CI)	p	HR (95% CI)	p	HR (95% CI)	p
Low CMV tertile	reference		reference		reference	
Medium CMV tertile	1.03 (0.79, 1.35)	0.815	1.40 (0.93, 2.13)	0.110	0.74 (0.52, 1.05)	0.090
High CMV tertile	1.03 (0.78, 1.35)	0.831	1.47 (0.93, 2.35)	0.101	0.80 (0.57, 1.12)	0.196

Cox model adjusted for sex, age, BMI, level of education, smoking status and pack-years.

Table S4: Associations between CMV tertiles and mortality by cancer defined as underlying cause of death on death certificate (“from”; a) or as either underlying cause of death or co-existing condition on death certificate (“from or with”; b).

Mortality from cancer (a)	All subjects (N=783)		<55 years (N=387)		≥ 55 years (N=396)	
	Deaths=139		Deaths=78		Deaths=61	
	HR (95% CI)	p	HR (95% CI)	p	HR (95% CI)	p
Low CMV tertile	reference		reference		reference	
Medium CMV tertile	1.30 (0.83, 2.05)	0.249	1.39 (0.76, 2.53)	0.284	0.88 (0.44, 1.77)	0.730
High CMV tertile	1.87 (1.20, 2.90)	0.006	2.53 (1.44, 4.46)	0.001	1.18 (0.60, 2.33)	0.624
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Mortality from or with cancer (b)	All subjects (N=783)		<55 years (N=387)		≥ 55 years (N=396)	
	Deaths=149		Deaths=81		Deaths=68	
	HR (95% CI)	p	HR (95% CI)	p	HR (95% CI)	p
Low CMV tertile	reference		reference		reference	
Medium CMV tertile	1.20 (0.78, 1.84)	0.408	1.37 (0.76, 2.45)	0.289	0.80 (0.42, 1.52)	0.489
High CMV tertile	1.64 (1.08, 2.51)	0.021	2.36 (1.35, 4.10)	0.002	1.01 (0.54, 1.89)	0.982

Cox model adjusted for sex, age, BMI, level of education, smoking status and pack-years.

Table S5: specific cancer mortality and CMV tertiles

Lung	All subjects (N=783)	
	Deaths=36	
	HR (95% CI)	p
	Low CMV tertile	reference
Medium CMV tertile	1.49 (0.63, 3.50)	0.360
High CMV tertile	1.54 (0.65, 3.64)	0.321
Colon and rectum	All subjects (N=783)	
	Deaths=12	
	HR (95% CI)	p
	Low CMV tertile	reference
Medium CMV tertile	0.21 (0.22, 2.01)	0.176
High CMV tertile	2.16 (0.54, 8.64)	0.276
Liver	All subjects (N=783)	
	Deaths=13	
	HR (95% CI)	p
	Low CMV tertile	reference
Medium CMV tertile	1.67 (0.38, 7.41)	0.498
High CMV tertile	1.68 (0.37, 7.64)	0.499
Breast	All subjects (N=783)	
	Deaths=15	
	HR (95% CI)	p
	Low CMV tertile	reference
Medium CMV tertile	0.92 (0.23, 3.64)	0.910
High CMV tertile	1.63 (0.45, 5.85)	0.456
Hematological system	All subjects (N=783)	
	Deaths=12	
	HR (95% CI)	p
	Low CMV tertile	reference
Medium CMV tertile	3.27 (0.63, 16.9)	0.157
High CMV tertile	2.53 (1.11, 15.0)	0.307
Urogenital systems	All subjects (N=783)	
	Deaths=24	
	HR (95% CI)	p
	Low CMV tertile	reference

Medium CMV tertile	1.44 (0.37, 5.64)	0.596
High CMV tertile	5.94 (1.77, 19.9)	0.004

Cox model adjusted for sex, age, BMI, level of education, smoking status and pack-years.

Figure legends

Figure S1: Estimated hazard ratios for the association of high CMV serology with cause specific mortality by age at enrollment.

Estimates from three separate Cox models for COPD, cardiovascular and cancer mortality adjusted for sex, age, BMI, level of education, smoking status and pack-years and including interaction terms between CMV serology tertiles and age at enrollment.

Figure S2: Covariate-adjusted survival curves for all-cause mortality among the 113 TESAOD participants with airflow limitation at baseline, plotted by CMV tertiles. P values refer to trend across CMV tertiles.

Total number is lower than 116 included participants with airflow limitation because some individuals had missing information on covariates. Curves adjusted for sex, age, BMI, level of education, smoking status and pack-years. Body mass index (BMI) was categorized as follows: underweight: BMI <18.5 kg/m², normal weight: BMI 18.5-24.9 kg/m², overweight: BMI 25-29.9 kg/m² and obese: BMI ≥30 kg/m². Level of education was categorized as ≤12 years or >12 years of formal education.

All-cause deaths=106. Medium vs low CMV tertile HR: 1.76, 95% CI: 1.02-3.06, p=0.043; high vs low CMV serology HR: 2.10, 95% CI: 1.20-3.68, p=0.009;